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CONTENTS

THE RÔLE OF HEREDITY IN DISEASE

MADGE THURLOW MACKLIN, A B , M D

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1. INTRODUCTION

Although the rediscovery of Mendel's work placed the observations of botanists and zoologists with respect to hereditary qualities of plants and animals upon a firm scientific basis, it afforded less encouragement to those who were interested in the so-called "hereditary" characters of man   The most essential experimental method available to the scientists studying heredity, namely, experimental matings, was by its very nature denied to the students of human inheritance

Perhaps belief in the hereditary nature of characters in man was more strongly intrenched before the rise of modern genetics than it was in the two decades following the rediscovery of Mendel's theory This was especially true in the realm of disease, for it was far easier to determine the thread of inheritance of a trait that marked an individual off from the rest of mankind, than it was to trace the descent from parent to child of a quality which was universal in the population   For this reason, there were numerous pedigrees compiled to show the hereditary nature of a few rare diseases years before there were any scientific data available dealing with the mode of transmission of normal characters

2 EARLY CONCEPTIONS OF HEREDITY IN DISEASE

Illustrating this point, we find an elaborate pedigree furnished by Sir William Herringham (1) of a family some of the members of which were victims of a very rare malady, peroneal atrophy   Through four or five generations this strange thread had woven itself into the warp and woof of the life of these people, and although naught was known of sex-linkage in those days, Herringham's record is of a disease which unerringly picked out the males, and left the females unscathed

Stranger still, the sons of these affected men were wholly free as were their children, and their grandchildren from the curse But like the hand of an avenging fate, the dreaded malady fell upon the sons of the women, who although free themselves, yet were to know the agony of seeing their loved ones fall victims to the condition

Just as spectacular, but much more common is the condition which has run in similar manner through the families in which the boys die of hemorrhage, and the women are free of the disease This is of particular interest, for it is a disease which has marked royalty as its victims

Even as we find authentic records of hereditary diseases before there was any knowledge of the mechanism of transmission of inherited traits, other than that "it ran in the family," so we find diseases not hereditary, erroneously so labelled for the very same reason, that it ran in the family Thus syphilis, the etiology of which was unknown, was incorrectly spoken of as "hereditary," and is still so called by many clinicians

For many years tuberculosis was regarded as hereditary because of its predilection for certain families, and it was not until the discovery of the tubercle bacillus by Robert Koch that its transmissibility by germs rather than by germ plasm was established beyond doubt. With the advent of bacteriology, ideas as to the hereditability of disease steadily lost ground, as one disease after another was found to be due to microorganisms But the pendulum has begun to swing back again, and as it swings, gathers more than tuberculosis into its arc It is true that many of these diseases are due to bacteria, but not all persons nor all animals encountering these bacteria develop the disease There is a second element the susceptible soil upon which the bacteria may grow, which is necessary before the disease is outspoken There is gradually accumulating evidence which shows that this susceptibility or immunity, as the case might be, is hereditary Thus the negro is especially prone to develop tuberculosis This might be attributed to his living in crowded, unhygienic surroundings, but on the other hand he is less susceptible to skin diseases, or to respiratory diseases with an exanthematous manifestation than is the white man, yet the same crowded environment might in this case, as in that of tuberculosis, predispose toward a high incidence in the

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negro race   Many other diseases, now looked upon as dependent
entirely upon microorganisms, will probably be shown ultimately to
be related also to the hereditary suceptibility and immunity of the
persons coming into contact with the infecting agent   Some families
have an unusually high death rate from pneumonia, although the
deaths do not all occur at the same time, so that contagion due to
the immediate presence of the disease in the family may be ruled out

Not only did clinical observers make accurate deductions as to the
hereditary nature of diseases which we still regard as hereditary in
the light of modern genetics, not only did they erroneously designate
as hereditary some diseases which are not so regarded, or whose
etiology cannot be looked upon as exclusively hereditary in the light
of modern bacteriology, but they also failed to recognize as inherited
many diseases which are hereditary, but which were and still are not
universally so interpreted, because the clinical observer is unfamiliar
with the data of modern genetics which permit of such an explanation
To bring forth some of the obstacles which have stood in the way of
correctly interpreting the hereditary nature of these conditions is the
object of a portion of this paper

3 THE RISE OF MODERN GENETICS

Shedding its light over this mass of empirical observations, the sun
of modern genetics rose in the scientific sky, and all data dealing with
heredity now had to be scrutinized under this new light   Facts which
were inexplicable before in botany and zoology were seen to be the
outcome of well defined laws   It became evident that what was put
into a mating, sometimes latent, sometimes obvious, came out in the
offspring with mathematical precision   Experimental matings were
made to determine the operation of the laws of heredity, the mode of
transmission of various characters, and their modifiability in the
presence of other characters   Rapidly genetics grew into a science
as precise and exact, and governed by as well defined laws as chemistry
or physics   We knew that if we put certain amounts of chemically
pure substances into a retort, under controlled conditions of light,
temperature, moisture, etc , we could predict with unerring accuracy
the results we would obtain   So it came to be with genetics   If we
put genetically pure parents into the crucible of mating, we could
foretell what the offspring would be

Then occasions arose when the predictions failed to materialize Something seemed to have gone wrong. Was it that transmission of hereditary characters was not governed by such infallible laws as we had thought? Not at all. It was merely that not knowing all of the facts, we had not made the law sufficiently comprehensive. Here cytology came to the aid of the geneticist, in the interpretation of his results. Examination of the chromosomes in the germ cells of these forms, which when mated had yielded the unpredicted results, afforded further evidence to show that upon the chemical and physical structure of these minute bodies rests practically the entire developmental potentiality of the individual. Genetics combined with cytology was now able to explain "crossing over," "linkage," "translocation," etc. Chromosomes were found to be large packets of individual genes or determiners strung like beads on a string, the same genes occurred in the same chromosome in members of the species. Those occurring in the same chromosome were said to be linked, because they were all transferred into the mature germ cell in a group in the one chromosome. Many different traits were found to have their genes in the same chromosome, and strangest of all, sex was found to be an inherited character dependent upon chromosomes just like any other individual trait. And because of the unequal distribution between the sexes of chromosomes regulating sex, linkage of many other traits with sex was found. This offered an explanation of many of the hitherto inexplicable findings in experimental matings.

Thus gradually the geneticist was able to unfold an amazingly accurate map of the chromosomes of the form with which he worked, maps showing not only that a character was hereditary, but what chromosome in the germ cell had the determiner for that character in it, and where along the length of the chromosome the determiner was located. Moreover, he was able to say just what genes lay on either side of it, and how the presence of these genes was able to modify the original character whose heredity was being investigated

a Limitations of the application of genetics to human heredity

All these elaborate studies made upon plants and lower forms of insect life only served to emphasize the gulf that lay between genetics as a science and its application to the problems of human inheritance In man, the matings were random, not controlled, the genetic con-

stitutions of the parents entering into the mating were unknown, the breeding period was so delayed that it was seldom that any one scientific observer could watch the effects of the condition upon more than two generations, the number of the offspring was so limited that there were seldom enough children to express all the possibilities of the mating with respect to any one character, experimental matings could not be made to test out any theory as to the mode of transmission of the character, cytological evidence of the behavior of the chromosomes was lacking in every instance with the exception of the number of the sex chromosomes   The student of human inheritance was thus limited to the observation of an experiment which he had not planned, about the beginnings of which he knew nothing, and the course of which he could not control   Any deductions which he might make could not be verified, much of the evidence upon which these deductions would rest would be hearsay evidence gathered by workers not trained to observe accurately   For these reasons many geneticists refused to countenance any belief in heredity in human characters, not because they did not believe that human beings inherited their normal or abnormal traits, but because there was no scientific evidence in favor of such a belief

It is true that human genetics is not an exact science in the sense that genetics dealing with plant or animal life is a science, but there are certain scientific modes of approach to the subject, which, used in combination with each other, yield information that is valuable   It is unreasonable to reject this information because it is not gained in the way usually employed in the study of genetics

4 GENETICAL TERMS AND CONCEPTS

Perhaps at this point it will be wise to pause for a few moments to discuss in a most elementary form some of the principles of genetics, so that the terms used later on may be more fully comprehended   It will be impossible to give adequate discussion of the subject, and reference must be made to the text-books dealing with genetics, which go into the proof, both genetic and cytologic, for all the concepts which have sprung into being concerning this youngest of all the biological sciences (2, 3)

It is well known that the only thread which links one generation

with the next, especially in those forms in which the female does not
retain the developing embryo within its body, is the germ cell which
once constituted a part of the body of the parents, and which now
becomes the starting point of the new individual   Like all true cells,
the germ cells possess both nucleus and cytoplasm   In the prepara-
tion of these cells for fertilization they undergo certain peculiar changes
not experienced by any other of the somatic cells   These changes
involve both cytoplasm and nucleus, but more particularly the latter
Thus the male germ cell loses practically all of its cytoplasm, yet it
appears to contribute as much to the hereditary qualities of the off-
spring as does the female, which retains practically all of its cytoplasm
Both male and female cells undergo well defined changes which are
almost identical in the two sexes, and which have as their aim the
exact division of the nuclear chromatin into two equal parts

a Maturation

The nuclear chromatin of all cells undergoing mitosis becomes aggre-
gated into masses known as chromosomes   Each chromosome be-
comes split longitudinally into equal halves, which separate, thus
affording the daughter cells not only an equal quantitative but an
equal qualitative representative of each of the original chromosomes
In maturation of the germ cells, a still further modification of the
chromosomes takes place   The number of chromosomes is constant
for the species, and can be represented as $2n$ There are n pairs of
chromosomes, each pair being known as a pair of allelomorphs   One
chromosome of each pair came from the paternal parent of the in-
dividual, the other from the maternal parent   The further modifica-
tion, which was just stated to occur during maturation, is the actual
separation of the paternal and maternal members of the pair   *One*
and *one only* of the pair goes into the maturing germ cell, the other is
irretrievably lost to that mature cell   In this separation of the allelo-
morphs after conjugation in meiosis lies most of the secret of genetics
It is because of this that combinations and recombinations can be
made, that some children inherit one trait, while others in the family
inherit a different character, yet because of the chance that some will
inherit the same chromosome from the allelomorphic pair, there is the
opportunity for children of the same family to resemble each other

more closely than they do outsiders Thus it provides diversity within similarity.

Concerning the more technical aspects of the subject such as crossing over of chromosomes, translocations etc , we will say nothing The cytological evidence upon which these conceptions are based has not been established for human germ cells But of some of the simpler aspects of inheritance we must say a few words in order that the use of the terms in later discussion may be clear

The essential process accomplished by maturation of the germ cells, namely, the elimination from the mature germ cell of one member of each pair of chromosomes, has reduced the number of chromosomes by one half, so that after fertilization the other germ cell, having undergone a similar maturation, will bring in half of its chromosomes and so restore the original number Thus when the new zygote starts development it will have the same number of chromosomes which its parents had, and they again will be in pairs, one of which will have come from the maternal, the other from the paternal parent Just as the maturation process in the germ cells, which resulted in this new individual, separated the allelomorphs which were present in the egg and sperm cell, so when the germ cells of this new person mature, the paternal and maternal chromosomes will again separate, only one going into the cell which is to start the next generation Thus some of the hereditary characters would be completely lost, others would persist through generation after generation

b Dominance and recessiveness

Another fact which we must understand, but which is not an essential part of the mechanism of heredity as is the segregation of the characters just described, is the one which has to do with the so-called dominance and recessiveness of traits The hereditary potentialities carried in each member of a pair of chromosomes have to do with the same developmental traits, although they may differ as to details of that development Thus both maternal and paternal allelomorphs forming a pair of chromosomes will carry a gene for hair color, but one may carry a gened which determines little pigment in the hair, while the other carries a factor for heavily pigmented hair On the other hand, the genes from both parents may be identical   When

both parents contribute exactly identical genes to the fertilized zygote, the resulting individual is said to be a homozygote or to be pure for that particular trait, inasmuch as his germ cells, in their process of maturation, can give only one type of germ cell with respect to that particular gene   When the two parents contribute genes differing in their quality, as for example, when one contributes a gene for lightly pigmented hair, the other a gene for heavily pigmented hair, the resulting individual is said to be a hybrid or heterozygote because his germ cells, in the process of maturation, can produce two types of mature cells with respect to hair color   The gene for light hair or the gene for dark hair may be the one left in the mature cell after the separation of the allelomorphs in the reduction division, and the chances are equal that, either gene will be left in the cell   Such a person can pass on two factors for type of hair   It is evident that persons pure for hair color might be pure either for dark or for light hair   Thus we could have three types of persons, one pure for light, and capable of passing on only one type of hair color, one pure for dark and capable of passing on only one type, namely dark, and one hybrid capable of passing on either light or dark in equal proportions

But what does such a person who is a hybrid show? Is the hair light, dark or intermediate between the two? The answer to such a question depends upon the trait in question, and upon the species of animal life being described   For some traits, the hybrid form is intermediate between the conditions shown by the two parents   Thus some flowers, one of whose parents was pure for red, the other pure for white, will show a pink color, or red diluted with white   Other species, under the same conditions will show undiluted red in the hybrid form, that is, the fact that white is present will be concealed   When one quality is able to suppress another in the hybrid form, it is said to be *dominant* over the other quality   When a quality is capable of being suppressed by the presence of another, it is said to be *recessive* to the dominant quality   From this it follows that a dominant quality will show in the individual who possesses it, both when the possessor is pure or homozygous for it, and when he is hybrid or heterozygous for it   On the other hand, the recessive quality, in order to be evident as such must be present in the pure or homozygous form, since the presence of the dominant quality is enough to suppress it

Table 1 shows the six possibilities of mating individuals who are homozygous or heterozygous for any one set of characters If the letter D be used to express dominance, such as red in the flower, and R recessiveness, such as white in the flower, then the possible matings are as shown in this table

Several facts become obvious from a study of table 1 The first is that in a community of red and white flowers, where cross pollination was possible, one would have far more red flowers resulting than white, inasmuch as in three of the six matings only red flowers result, in one mating, red occurs in half the offspring, and in one mating, red occurs in three-fourths of the offspring. White occurs in one mating

TABLE 1

| | PARENTS | | OFFSPRING |
	Male	Female	
1	DD (pure red)	DD (pure red)	DD (pure red)
2	DD (pure red)	DR (hybrid red)	DD (pure red), DR (hybrid red)
3	DD (pure red)	RR (pure white)	DR (hybrid red)
4	RR (pure white)	RR (pure white)	RR (pure white)
5	DR (hybrid red)	RR (pure white)	DR (hybrid red) and RR (pure white)
6	DR (hybrid red)	DR (hybrid red)	DD (pure red), RR (pure white) DR (hybrid red), DR (hybrid red)

exclusively, in half the flowers of another, and in one-fourth of the flowers of a third If we imagine free mating between the three types, DD, DR and RR, and if we imagine the same number of flowers to result from each of the matings, we find that 75 per cent of the flowers in the garden will be red, while 25 per cent will be white Thus it is easy to understand how, in a country where the population is a mixed one, dark hair and dark eyes, both of which are apparently dominant over the conditions of light hair and blue eyes, should occur much more frequently than do the latter

Another fact to be noted is the important one now to be discussed In the first five matings, it will be seen that the offspring resemble at least one, sometimes both parents Thus the heredity of the condition is easily understood, since offspring looks like parent In

mating 6 on the other hand, both parents are red, and there is no indication of the fact that they conceal a gene for white   One quarter of their offspring is like neither of them, being white   Here is a trait showing up in offspring, which was apparent in neither of the parents, and so it is apt to be regarded as not hereditary, since the transmission from parent to child is obscured   Yet it is as truly hereditary as is the red condition which the other three-fourths of the offspring in this mating show   It was transmitted by both parents to this offspring, and must be classified as an inherited character, even though for many generations back, its ancestors may have been red flowers   It is this type of hereditary transmission which has confused the issue with respect to heredity in man, and which has led to the erroneous conceptions that conditions which appear in offspring whose parents did not show them are not hereditary but "familial "   This will be taken up more fully a little later

c Inheritance of sex

We are not in the habit of looking upon sex as an inherited quality in the same sense that eye color, or stature or mental ability is inherited   Yet if we remember that the definition of "hereditary" is that the character in question must be passed on in the germ plasm from parent to offspring, then sex is hereditary   If such a character shows segregation, it must be dependent upon factors in the chromosomes, hence we must recognize that sex is connected with the chromosomes   The special chromosomes which are responsible for sex in man are the only ones so far which have as yet been definitely identified with the inheritance of any special character in the human being

The latest conception of sex chromosomes in man will be referred to briefly   It has been stated that there are a definite number of chromosomes characteristic of the species in each of the cells of an organism   These are arranged in pairs   One of these pairs is concerned with sex   In the female, both members of the pair are alike as far as shape and size and determining sex are concerned, and in the maturation of the ovum, it does not matter which one is retained in the ovum and which one is lost in the polar body, for with respect to the determination of sex, they are identical   In the male, however, this is not true   The pair of chromosomes concerned with determining sex, differ in

size and in shape, and one of them carries, so far as is known, no genes for the determination of any characters whatever. One of the pair is like the sex chromosomes in the female, the other member is smaller, and is the one which is not the carrier of genes. When the spermatocytes of the human being undergo their reduction division, that is, when one of the allelomorphs from each pair is lost to the mature cell, the resulting spermatids are of two types with respect to the sex chromosomes. One-half of them contain the chromosome that is like the sex chromosomes of the female, the other half contain the sex chromosome which differs from its mate, and from those in the female.

In the process of maturation, the sex chromosomes kept themselves somewhat apart from the other chromosomes, and acted independently of them, hence they were named the X or unknown chromosomes. Later the term "X" was changed to sex chromosomes, when their function was discovered. Using this terminology now will simplify the further discussion. The female has two X chromosomes in the oogonium, one X in the mature ovum. The male has one X and its mate or allelomorph named Y, because it was dissimilar in form. If the sperm which contains the X chromosome fertilizes the ovum, the resulting zygote will have two X, and therefore the cell develops into a female organism. If the sperm with the Y chromosome fertilizes the ovum the resulting zygote has an XY, the chromosomal complex which we found to be characteristic of the male, and into a male such a cell develops. Thus the sperm is the determining factor as far as the sex of the human embryo is concerned.

So far, we have considered each chromosome as if it were concerned with the transmission of but one character or trait. But when we remember that, in man, there are only forty-eight chromosomes, we can readily see that each one must carry far more determiners for hereditary qualities than just one. In Drosophila this has been shown to be the case, and it may be that several hundred individual genes are carried in one chromosome. Those that are gathered in linear order in a chromosome are said to be *linked,* and because of the outstanding nature of the character carried by the sex chromosome, namely sex, it has been possible to find some traits, mostly abnormal it is true, that are carried by the sex chromosome in addition to sex. These are the only definite examples of linkage discovered so far in man.

The traits whose genes have been shown to be located in the sex chromosomes have proved to be all of one type, namely recessive in character   It is quite probable that there are dominant abnormal factors also located in the sex chromosome, but because of the less spectacular distribution of these, they have not been so easily identified   Due to the recessive nature of the abnormal traits which will be taken up later, it is impossible for them to become evident as such so long as there is a gene for normality in the allelomorphic chromosome   Inasmuch as the female has two sex chromosomes, there is of course less opportunity for the recessive abnormal trait to be present

TABLE 2

| | PARENTS | | OFFSPRING | |
	Female	Male	Female	Male
7	DD (normal)	× D (normal)	DD (normal)	D (normal)
8	DD (normal)	× R (affected)	DR (normal hybrids)	D (normal)
9	DR (hybrid normal)	× D (normal)	DR (normal hybrids)	R (affected)
			DD (normal)	D (normal)
10	DR (hybrid normal)	× R (affected)	DR (normal hybrids)	D (normal)
			RR (affected)	R (affected)
11	RR (affected)	D (normal)	DR (normal hybrids)	R (affected)
12	RR (affected)	× R (affected)	RR (affected)	R (affected)

in double dosage than there is in the male who has but one sex chromosome carrying genes, and who therefore is able to show the recessive trait as such when it is present in but single dosage

Table 2 shows the possible matings when the sex chromosome is carrying a recessive abnormal trait   If R denotes the recessive trait, which cannot express itself in the body of the individual so long as there is a D or dominant normal gene to offset it, and the female having two sex chromosomes has to have two letters to denote the constitution with respect to the character, and the male, having but one, needs but one letter, we get the series of matings as shown in this table

Again analysis of the table brings out several generalizations   (1)

When both parents are pure for normality, none of the offspring are affected   (2) A normal woman mated to a man with a sex-linked recessive trait has all her offspring normal, the sons completely so, the daughters normal but carriers, capable of having affected sons as shown by the next mating   (3) A woman who is a carrier or hybrid for a sex-linked recessive disease who marries a normal man, will have all her daughters normal, but the chances are that half her sons will be affected, half normal   (4) When a woman who is a carrier mates with a man who is actually affected, half her sons are apt to be normal, half affected, and half of her daughters will be apt to be affected, half to be normal but carriers   (5) When a woman who is affected marries a man who is normal, all her sons will be affected, and all her daughters will be hybrids   (6) When a woman who is affected with a sex-linked recessive disease, marries a man similarly affected, all the offspring will be affected.

Now it will be noted that in order for a woman to show a sex-linked recessive character, the father himself must be affected, and the mother either affected or a carrier   If the condition in question be a rare one, then such conditions are apt to be fulfilled only when the parents are related   Another point to be noted is that such a trait will show up in a male to whom it has descended through generation after generation of unaffected female carriers, thus appearing in him perhaps with no previous history in the family   Finally, such a mechanism of inheritance permits of twice as many males being affected as it does of females showing the trait   Later on we will come across many defects and diseases, not limited to the male generative organs, which are almost exclusively male in their distribution   Such are very apt to be sex-linked recessive or to be dependent upon a group of factors some of which are recessive and situated in the sex chromosome

5 MISCONCEPTIONS CONCERNING THE MEANING OF "HEREDITARY"

a Congenital

Having gained some idea of the mechanism by which hereditary characters are transmitted, it will be well to clear the atmosphere of a few misunderstandings which obscure the nature of heredity, es-

pecially in the minds of those not trained to any extent in the science
of genetics   Thus many confuse the terms *congenital* and *hereditary*
They feel that for a character to be hereditary it must be congenital,
or make its appearance shortly after birth   If it does not, then it is
thought not to be hereditary, and that at most a predisposition toward
its development exists   If such a conception be admitted, then we
must go further back, and realize that birth is but a step in the un-
folding of the individual, and that if a quality is to be hereditary, it
must be present as such at conception   When we have reached this
reductio ad absurdum, and see that after all, we inherit nothing as
such, but inherit merely the predisposition to develop in a certain
manner under given circumstances, we are able to appreciate that an
inherited trait may be one which does not develop for years after
birth   It is well known that longevity is an inherited trait which
characterizes some families, yet it is one that of necessity requires a
very long life to prove its existence

In cattle breeding the trait of milk production is one that is known
to be distinctly hereditary, yet it is one which not only is *not con-
genital,* but is dependent upon the circumstance of pregnancy to call
it forth   Thus congenital and hereditary are terms which are neither
mutually exclusive nor inclusive

b Familial

A second misconception is that which allows the clinician to designate
some diseases as "familial" others as "hereditary," as if the familial
disease was not an inherited one   By the first term, he understands
those conditions which appear in several children of the family with-
out there being any earlier history of it in the ancestors   By the
latter he means those diseases which have come down from parent to
child through several or more generations   Now to the geneticist,
it is quite comprehensible that a trait should be present in the children
although there may have been *no signs of it in the forbearers*   Such a
trait is just as definitely inherited as is one which runs in uninterrupted
line through generation after generation   Example of the so-called
familial trait would be found in the white of the flower derived from
two red parents in Mating 6   The trait comes to the offspring through
both parents, neither of whom showed it but both of whom carried it

latent   Much misunderstanding concerning inheritance of disease will disappear when the clinician looks at these problems through the eyes of the geneticist, and interprets recessive traits as truly inherited, and not merely as familial

c The Mendelian ratio

A third stumbling block to the physician who is studying the inheritance of human traits, especially abnormal ones, is the failure to appreciate that the defect need not appear in the precise proportion of offspring which the laws of Mendel require   Thus one not infrequently finds statements in the literature to the effect that a character cannot be dominant because it does not appear in the 50 per cent of the cases expected when one parent is heterozygous for the presence of the dominant character, the other homozygous for its absence Let us examine the conditions under which these Mendelian ratios were obtained, and the reasons why they are not to be expected with such unerring accuracy in human matings

If one is dealing with a large number of female and male egg cells of any form, plant or animal, which are uniting at about the same time, and if there are two types of germ cells with respect to any one character, then an approach to the Mendelian ratio for such a mating is almost inevitable, for as one type of sperm is used for fertilizing any one type of egg, it is automatically removed from the possibility of entering into the process of fertilization again, and so the chances that the other type of sperm will enter into the next fertilization become higher   In human matings this is not true   Each time an ovum is fertilized, all the possibilities are again there to be realized, and there is no weighting of the chances for any one type of union to take place

An illustration will serve to make this clear   Imagine a box of twenty *balls* in which ten are black, ten white. Let these represent the male germ cells   Imagine another box in which are ten black *cubes* and ten white *cubes*   These will be the female germ cells   What are the possibilities of combining balls and cubes?   Black may combine with black or white, and white may combine with black or white If a person were blind-folded and were to choose a ball from one box and a cube from another and were to lay them on the table, one would

find that on the average five times
together, five times the white ball
times the black ball and white cub
black cube and white ball were pa
cubes and balls in the boxes, the
approximated   But it is quite obv
selecting black and white were eq
ment, as soon as a black ball was
were slightly in favor of a white b
fact they were 10 to 9 in favor of
the second choice, a black ball sho
the chances still higher in favor
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in favor of the white being the nex

But if the person who was playi
the balls to the boxes after he had
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choice that black or white would b
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but it is equally true that for any
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The first game played by the pl
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character, the parents might have but one child If the combination of white ball with white cube were the one which represented an abnormal trait in the offspring, that combination might be made in the first and only child, thus giving for that family, 100 per cent affected Or the opposite might be true The parents might have but one child, and the combination of black with black be made, illustrating complete normality They would be unaware of the existence of the sinister possibility of the two white factors combining, and that family would never know that it held an abnormal character, and so would never be used in a series of families for the determination of the ratio of affected to unaffected offspring Thus only such families as had made the combination of two white factors would be included in the series, which would thus be automatically weighted in favor of the abnormal trait appearing

An illustration of this weighting may be found in collected records of amaurotic idiots I found that in 118 families in which there were 509 children, there were 210 affected with amaurotic idiocy, an incidence of 41 per cent Since this condition is one which is recessive in character, hence comparable to the simultaneous choice of white ball and white cube, we should expect only 25 per cent of the children to be affected. We do not know how many families were capable of producing amaurotic idiots who had only normal children, which should have been included in this series along with the normal children of the families studied

Still another misunderstanding on the part of the clinical observers untrained in the fundamentals of some of the biological processes, is one based upon the belief that if a character is inherited, it must appear in all the offspring in the family Not fully aware of the processes of maturation or of their significance, they do not grasp the mechanism by which an affected person may under certain circumstances pass on his defect to one child, and not to another. Just as one might choose either the black or the white cube, but not both on any one choice, so the germ cell can contain either the chromosome carrying the gene for the defect, or the chromosome bearing the one for normality, if the parent is one who is heterozygous for the condition

6 VARIATION IN TYPE OF INHERITANCE

a Similar clinical entities due to diverse pathological conditions

Another point of confusion in the study of human genetics is that the character in question may behave as a dominant in one family and as a recessive in another Thus polydactyly which acts as a dominant in most families has been found to act as a recessive in others Peroneal atrophy was observed through four generations as a sex-linked recessive by Herringham (1), and as a dominant through five generations by Macklin and Bowman (4) The geneticist formerly took the attitude that if a trait was a dominant one in one family, it must be a dominant in all families, otherwise the diagnosis or the records were incorrect Now it must be remembered that the trait being observed may be dependent upon a half dozen different pathological conditions One of these may be inherited as a dominant, another as a recessive, and still a third may be linked in the sex chromosome Thus in diabetes, one may have sugar in the urine due to sclerosis of the vessels of the pancreas, or due to degeneration of the pancreatic islets, or due to inadequate development of the islets in the embryo, or due to the production of some hormone inhibiting the formation of insulin for the regulation of blood sugar It might conceivably be due to an inability on the part of the muscles to utilize sugar, or to a lesion in the nervous system which might regulate the secretion of insulin All of these would produce the symptoms of diabetes mellitus, and in some families the diabetes would behave as a dominant and in others as a recessive, due to the various genes determining the pathology of the condition

b Dependence on several genes in same chromosome

Another explanation of the diversity of the mode of inheritance of the same clinical symptoms in different families may be as follows Let us suppose that diabetes mellitus is dependent upon the presence of five genes, A, B, C, D, E These are all located in the same chromosome next each other in the linear series of genes Not unless all five are present will the disease develop as such Since the chromosome acts as an entity in the process of maturation, either passing as a whole into the mature cell or being lost, all five genes will either go

into the ovum, if the female cell is being considered, or into the polar body Hence their behavior will be comparable with that of a single determiner acting as a unit   Since their presence makes for diabetes and their absence for normal metabolism, the chromosome which contains them determines diabetes in the individual   When such a person reaches the age of reproduction, half of the offspring are apt to get the chromosome with the five factors, the other half will not receive this   Hence it acts as if due to a dominant determiner

Unless that chromosome were one in which splitting occurred somewhere in the middle of the diabetic group of genes, between C and D for example, with subsequent crossing over, one could not tell from the most carefully planned experimental matings that diabetes was not due to a single gene   Its transmission would agree with that of a dominant character   Here it might be remarked that many traits which have been looked upon as unit characters, may in reality be dependent upon several genes so closely linked in the same chromosome that splitting does not occur at that point   Such traits would be considered as units in their hereditary transmission

But suppose that due to a crossing over in some ancestor, or due to a primary lack of all five factors, we had an individual whose chromosomal make-up included only the genes A, B and C and that D and E were lacking   Such individuals would be free from diabetes   Were they to mate with a person who had D and E, but lacked the first three genes, they might have offspring who held all five of the necessary genes for the development of the disease   The possible combinations of genes would correspond with the combinations of black and white balls and cubes mentioned earlier   Because of the loss of one of each pair of chromosomes at maturation, the mature germ cell might or might not contain A, B and C, from one parent, and D and E from the other   Thus there are four possible combinations (1) a mature fertilized ovum which lacked all five genes, hence a person wholly free from the disease, (2) a cell containing A, B, C being fertilized by a sperm lacking the D, E, again a normal individual, but one with some of the necessary factors for the disease, (3) an ovum lacking the A, B, C fertilized by a sperm with D, E, hence a person free from diabetes but possessing some of the factors for it, and (4) an ovum with A, B, C, fertilized by a sperm with D, E, thus giving a person with all five

persons whether diabetes is a dominant or a recessive   The expectations are so different in the two cases, and are so widely different even for a dominant character, depending upon the constitution of the parents, that it is small wonder that reliable deductions are not gained by this method   Examination of Table 1 will show, for example, that the expectation of obtaining a dominant character in the offspring ranges from 100 per cent in the first mating, where both parents were homozygous for the dominant character, to 75 per cent in the last mating where both parents were heterozygous for it, to 50 per cent in the fifth mating where a heterozygote mated with one homozygous for its absence, an RR, to zero per cent in mating 4, where two homozygotes for its absence mated.   Each family will have to be treated as a unit, unless there is a very striking uniformity of behavior in the inherited qualities of the trait being investigated   The latter is the case with amaurotic idiocy, for there has, to my knowledge, not occurred a report of a family in which parents were affected   This is because the patient always dies in infancy, not living to the age of parenthood   It always behaves as if due to a recessive gene   It might have been regarded as due to a dominant mutation which occurred frequently in the Jewish race, were it not for the fact that consanguineous marriages are fifty times as numerous among the parents of amaurotic idiots as among parents of the general population   Dominant mutations would not be increased by cousin marriages, and the appearance of recessive traits is increased by this means

Hemophilia, in all instances in which the laboratory findings have confirmed the clinical diagnoses, is always transmitted as a sex-linked recessive   It is another trait which appears to be uniform in its method of inheritance   But diabetes mellitus may apparently be transmitted as a dominant through one family, and as a recessive in others   Grouping amaurotic idiocy cases together for statistical purposes may be sound, the same treatment of data on diabetes may be quite unjustified, and lead to erroneous conclusions   The statistical method if properly applied, with full knowledge of the trait in question, is very helpful.   If applied without a genetical understanding of the subject, it may give false results

Let us cite a few examples   One of the statistical approaches to

the subject of inheritance is roughly as follows Collect a group of persons who exhibit the trait whose heredity is under investigation Ascertain what percentage of their ascendants showed the same disease Collect a similar control group, as near as possible like the first in every respect except one, namely, that they did not have the trait in question Ascertain the percentage of their ascendants who had the defect If the two are approximately the same, then the conclusion is drawn that heredity plays no part in the etiology of the condition Were amaurotic idiocy to be investigated in such a way, the conclusion would be reached that heredity played no part, for the percentage of affected parents in each group would be zero, since such patients never live to the age at which they become parents Such a conclusion would be erroneous as we have shown, for other statistical methods lead us to conclude that it is a recessive trait

Hemophilia is another trait that is undoubtedly inherited The number of hemophiliac ancestors of hemophiliacs is practically nil, however Why? Because there is such an elaborate set of conditions to be fulfilled before a hemophiliac can become an ancestor of a hemophiliac descendant In the first place, he must live to be old enough to reproduce, a condition not often fulfilled before the technique of transfusion was instituted One family, in which this disease was present, showed 30 per cent of its hemophiliac males dead of hemorrhage before the age of 5 years Secondly the hemophiliacs must not only live to the age of reproduction, but they must marry and reproduce Here again we find the records showing a number of such persons who have lived to maturity who did not marry Thirdly, if they reproduce sons, the defect is not transmitted, they must have daughters, for it is to them that the defective gene is passed on Fourthly, the daughters must live to the age of reproduction, must reproduce, and must have sons Daughters will not show the defect, so it must be male offspring which they produce Now examination of mating 9 in Table 2, shows that the expectation is that half the sons would show the defect, but it is quite possible that the woman might have one or two sons, who each time received the factor for normal blood, rather than the factor for hemophilia from the mother, so that again the ancestor might lose his chance of getting hemophiliac descendants This woman must have such a large num-

ber of sons, that the law of chance may operate and insure a hemophiliac among them   Only when all these conditions are fulfilled would we find a hemophiliac able to trace his affliction to a direct ancestor   As these conditions seldom are fulfilled, it is seldom that we find this trait in the direct ancestry of the patient

8   METHODS OF STUDY IN HUMAN GENETICS

So far we have dealt in the simplest of terms with the mechanism of heredity, and have considered some of the misconceptions that have stood between the clinical observer and a complete understanding of what is known at present concerning the importance of heredity in disease   We will now attempt to show that despite the limitations imposed upon us by the material, by the lack of experimental data on human matings, by the often incorrect clinical diagnosis, and by the imperfectly constructed pedigree, there are certain avenues of approach which are open to the student of heredity in man   Some of the more simple ones will be discussed here, those that require a more detailed knowledge of statistical methods not available to the average clinician being omitted   These can be found in text-books (5, 6), dealing with statistical treatment of data such as one collects in medical records   We desire to emphasize here, however, that if we approach the problem and look at it through the eyes of the geneticist who understands the mechanism of heredity, of the clinician who understands the clinical manifestations of the disease and the variation in symptoms, and of the statistician who is able to extract from massed data what the clinician and the geneticist are unable to get from isolated observations, in other words if we focus upon the problem from these three angles, we will gain an insight that would be lacking were we to view it from the angle of any of the three observers alone

a   The incidence of consanguineous marriages

The incidence of consanguineous marriages among the parents of the persons showing a supposedly inherited trait may give us information not only as to its being inherited, but also as to the type of heredity exemplified in the trait in question   For example, suppose we are dealing with a character that is not obviously handed down

from parent to child, and hence which may not be considered as
hereditary   Let this trait be one which is very rare in the general
population   Since it is not being passed on in the direct line of descent,
hence not acting as if due to a dominant determiner, it must be due to
determiners which are either recessive, or multiple, with some of them
probably recessive   Inasmuch as persons who are related are more
apt to have genes which are similar, since they have common an-
cestors, than are persons not related, we would expect to find that any
condition which was dependent upon a recessive factor, R, would be
more frequent in offspring of cousin marriages than it would in the
general population   Phrasing the idea in a different way, we might
say that if one should find consanguineous marriages more frequent
among parents of children with rare diseases, than one finds among
parents of the general population, it is good evidence that the disease
in question is an hereditary one, and secondly that it is dependent
upon recessive factors   If the disease were due to a dominant factor,
consanguineous marriages would not be necessary to bring it out in
the offspring, hence we should not expect to find the incidence of
cousin marriages any higher than normal when a disease is descending
directly from parent to child

To test this relation of consanguineous marriage to the possible
heredity of disease, records of 131 families with amaurotic idiots were
collected   It was definitely stated that in 13 families, or 10 per cent,
the parents were cousins   The incidence of consanguineous marriages
in the general population is about 0 2 per cent   Thus marriages of
relatives occur 50 times as frequently in families where some of the
children are amaurotic idiots as occur in the rest of the population

In 19 families in which microcephalic children had been born, 4 or
21 per cent gave a history of the parents being first cousins   This
incidence is just about 100 times as great as one finds in the popula-
tion at large   Thus with respect to these two conditions (both of
which we know may occur in children, neither of whose parents showed
the defect, and which if inherited must show the recessive type of in-
heritance), we find a high incidence of cousin marriages, which is just
what would be expected if the disease were hereditary, and recessive
Therefore we have strong evidence that these conditions are inherited,
and are due to recessive factors, which must be carried by both parents
before the offspring can exhibit the condition in themselves

b Identical twins in the study of inheritance

A second method which is available to the physician for observing the effect of heredity in the production of abnormal characters is the detection of the same disease in monozygotic twins   As is well known, twins may be of several varieties; monozygotic, derived from the same fertilized egg, hence presumably with the same hereditary characters, and dizygotic, derived from two different eggs, and hence with somewhat different hereditary potentialities   The latter will be alike just as two children in the same family will be alike, and will differ from each other as two children in the same family are apt to differ   Weinberg (5, p 322) states that of all the twins born, one-fourth are identical, three-fourths are merely fraternal twins   Now the fraternal twins may be of the same sex, or of different sexes, so that in fraternal twins the following possibilities may be expected, one set of males and one set of females to every two sets of male and female twins   For every two sets of identical twins necessarily of the same sex, there will be six sets of fraternal twins, three of whom have the same sex, three of whom have the opposite sex   Thus we should find that any list of twins collected at random should contain five pairs of twins of the same sex to every three of unlike sex   Two of the five would be found to be identical, three of the five would be fraternal

Now we must remember that identical twins differ from fraternal in one very important respect, namely, they are identical in their heredity, while the fraternal twins are dissimilar   If we were collecting records of twins where both twins had some definitely known hereditary disease, we should expect to find the identical twins showing an undue preponderance, inasmuch as if one has the disease, the other must have it, since it is hereditary   In the case of the fraternal twins it may happen that both have it, but it is not a certainty as in the case of the identical twins   Examining the converse of this, we should state, that if we collect records of twins where both have the same defect or disease, and if in such a collection, we find that identical twins form far more than 25 per cent of the group, we are justified in concluding that the discrepancy between the observed ratio and the expected ratio was due to the list being weighted in favor of some factor that made the identical twins have the condition oftener than the fraternal

The only factor which could do that is heredity   Therefore our condition under investigation is one which has an hereditary basis

As an example take diabetes mellitus   In a list of 14 sets of twins which I encountered in the literature, both of whom had diabetes, there was only one set which differed with respect to sex   Thus 7 per cent were of unlike sex, while one should expect to find 37 5 per cent of unlike sex, were the character in question not inherited   There were 10 sets of twins definitely stated to be identical, an incidence of 71 per cent, almost three times as high as the normal incidence of 25 per cent   There were three sets where the sex was the same, but no statement was made as to their being identical or fraternal   With monozygotic twins occurring three times as frequently as they should, with dissimilarly sexed twins occurring only one-fifth as often as they should, we have excellent evidence that this list is weighted in favor of the twins which have the same type of heredity, and the conclusion is justified that diabetes has a definite hereditary foundation

Thus identical twins with the same condition may be used as proof of the inheritance of that condition when the problem is viewed from the angle of the three groups of workers outlined above   The geneticist contributes the idea of the essentially identical heredity, the clinician the information as to the rarity or the common occurrence of the disease, and the statistician an interpretation of the findings based upon the outlook of the other two   It must be mentioned here that if the trait under investigation is one that is so common that it is met with in practically all members of the population, such a method as that outlined is of no assistance   It can neither prove nor disprove the hereditary nature of the condition, it merely ceases to be a method applicable to the solution of that problem

At this point the significance of the membranes in the diagnosis of identical twins should be mentioned   It has been assumed in most instances that monochorial twins meant identical twins, but that dichorial twins always meant fraternal twins or litter mates   If we review briefly the formation of human membranes, we see that this assumption is not wholly justified   There are three possibilities of combination of membranes for identical twins, only one for fraternal   Since the outer layer of cells of the developing egg forms the chorion, and the inner cell mass the amnion and the embryo, it is true that

fraternal twins must always be dichorial as well as di-amnionic   On
the other hand, it is not necessary that all dichorial twins be fraternal,
some of them may be identical   There may be identical twins who
are in the same amnion, as well as in the same chorion, a condition
that must be fulfilled before the twins can be joined   This type of
twinning occurs when the splitting occurs in the embryonic disc, after
the formation of the inner cell mass but before the formation of the
primitive streak   The second type of membrane combination occurs
when there are identical twins, each in its own amnion, but in the
same chorion   Here the splitting occurred earlier in development,
and two inner cell masses, with two resulting amnions, were formed
The third possibility is that after the fertilized egg has divided into
two daughter cells, these become separated, as can happen in lower
forms, and each develops its own chorion as well as its own inner cell
mass   Thus we would have identical twins that were *dichorial*

On the other hand, in twins that were dichorial, and fraternal, there
may be fusion between two adjacent layers of the two chorions, and
the two placentae may fuse due to crowding together in the uterus
Thus they may appear to be monochorial with two amnions, and the
obstetrician may consider that he is dealing with identical twins
Unfortunately, the significance of membranes in the diagnosis of iden-
tical twins, and the significance of identical twins in the study of
human inheritance have not been sufficiently appreciated, so that
records are not infrequently made that are in direct opposition to
genetic interpretations   If they are correct, then the genetic inter-
pretation must be altered so as to take cognizance of the facts, but
the difficulty is that we cannot always be sure that they are facts

For example, to the obstetrician not trained in genetics, there is
nothing incongruous in recording as monochorial, twins of opposite
sex   To the geneticist such a thing is impossible, and he would at
once investigate carefully any set of membranes which appeared to be
one, knowing either that they were two, or that he had a condition
there which would shake the very foundations of genetics

The physician might leave a record of monochorial twins, one of
whom was an anencephalic male, the other a normal male   If an-
encephaly be due to inherited defects in the germ plasm, such a record
is most disconcerting, but if the obstetrician made a mistake and

diagnosed as monochorial twins, what were really dichorial, then the record is simple

The importance of twins, both fraternal and identical, for inheritance studies are most important. The medical profession should be made aware of this importance, and should be encouraged to report every case of twins, where either one or both are affected with some disease or abnormality. They should also state as far as is possible, whether they are fraternal or identical, the age of onset of symptoms in the affected persons, and any points of identity or dissimilarity between the disease processes in the twins. When the medical profession has become thus trained, the interest in recording the condition of the membranes will necessarily follow, so that more accurate records in this respect will be obtained

c Pedigree method

Still another method is open to the student of human genetics, and it must not be disregarded merely because it does not have the lure of the mathematical approach. He may investigate the family history of the patient with respect to the occurrence of the same trait in other members of the family. This method is open to many objections, especially with respect to some traits, but it is nevertheless a *sine qua non* of human heredity studies. If the trait in question is one which requires no diagnosis on the part of a skilled physician, and no subjective estimation on the part of the observer, if it is one which was present at birth and easily observable, it is astonishing how frequently the pedigrees, as offered by a patient who has no genetical training, and who, therefore, cannot be accused of trying to make facts fit the theory, actually conform to the rules of transmission as evolved by the geneticist

For example, the presence of six fingers is a trait which is easily observed, which does not require the diagnosis of a physician, which does not entail a judgment on the part of the observer as would be the case for instance were one asking whether a patient was or was not mentally deficient, and finally it is a trait which is present at birth. With such a defect, one finds that the pedigree derived after careful investigation shows very close agreement with what one would expect to find if the condition were dependent upon a unit dominant factor. Even here,

however, one must remember that X-rays may show a metacarpal bone that is bifurcated at the tip, and which indicates the possibility of a sixth digit, without it actually being present as an accessory appendage on the hand. A pedigree showing the occurrence of polydactyly is apt to be accurate, and fairly easily analysed

But consider a trait which does not appear until late in life so that frequently the person who has inherited it may die before it develops, which requires the diagnosis of a physician, or even an autopsy to verify the presence of the condition. Such a trait is apt to be regarded as non-hereditary if rare enough to be seldom found, because of the difficulty in working out the descent from parent to child, or to be regarded as non-hereditary if common enough to be found in a large part of the population. The presence of tumors may be used to illustrate both these conditions. Tumors are a disease for the most part of old age, or of late middle life. Half of them occur after 60. Therefore many persons in the family tree, who would develop the tumor if they lived long enough, die before the tumor appears, and so such persons are listed as free in the pedigree. This materially interferes with the evidence of descent from ancestor to descendant. Again the symptoms from an internal malignant growth may be attributed to other conditions, and the diagnosis of malignancy never be made. Not infrequently has a diagnosis of pneumonia covered the presence of a primary or metastatic growth in the lung. Or in this connection especially, another circumstance arises which often destroys the obvious thread of inheritance. This is the fact that a tumor may occur in a tissue which is found only in one sex, although the gene for the development of such a tumor may have come to the patient from the parent of the opposite sex. Thus a woman may have carcinoma of the uterus. That gene may be transmitted to her son, who lacking uterine tissue does not develop a tumor. He may in turn pass on this gene to his son rather than to his daughter. It may finally become evident again in the great-granddaughter of the woman who first showed it, but because of the break of two generations in the meantime, it may be looked upon as mere chance that two women in the family had uterine carcinoma.

Such transmission of hereditary characters through a sex incapable of showing the character is of course known to the dairy herd breeder,

who selects the sire from a milk producing strain with the same care that he chooses the female parents from a breed of good milkers When we consider, moreover, that 35 per cent of all tumors, as shown in Pack's analysis of nearly 17,000 cases, occur in organs common to only one sex, we can understand why it is difficult frequently to trace the thread of inheritance of tumors

It was mentioned that one of the factors which worked against the acceptance of the idea that a condition was inherited might be that the condition was a very common one   Again we may cite tumors as an example   Because tumors occur in so many of the population, it has been difficult to show that they are hereditary   The argument of course has been as follows   "One in every ten, or nine or eight as the case may be, will die of cancer   On the basis of chance we would expect to find several members in the same family dying of tumor, nor would even five persons in the family with tumor be outside the realm of probability on chance alone   Therefore to find several members of a family with cancer is no proof of heredity "

The more specific fallacies which lie in this argument will be briefly taken up under the discussion of inheritance of tumors, but the general fallacy which is present in all such arguments is this   The universal presence of a condition throughout the population has been interpreted as evidence that the condition is not hereditary   It should merely show that obtaining proof of its inheritance is a difficult matter   For example, we know that the inheritance of five digits on the hand is an inherited character in man, but so universal is it that its heredity is lost sight of, until some abnormal trait, such as six fingers makes its appearance and proves to be inherited, whereupon the normal condition is shown to be hereditary also   Thus when we find tumors in one of every ten persons, we cannot thereby conclude that heredity plays no part in the etiology, the proof of that heredity merely becomes a more difficult matter

Another point in which the pedigree method has been thought to be of little value is in the instances in which only a few persons in the family can be shown to be affected   The trait may be one that is rare, and that is recessive in transmission, so that there may be no forbears with the disease   Depending upon the rarity of the condition in question, the presence of the defect in two members of the family in several

families may be sufficient from the statistical angle to prove the hereditary nature of the disease   The experimental geneticist, able to get any number of matings desired, is apt to insist upon a lengthy pedigree as an essential   The statistician, aided by the physician in estimating the rarity of the disease, may show that a defect is one which is met with only once in every 10,000 persons in the population   Were it dependent upon chance alone, it would occur in two members of a family once in $10,000^2$ or 100,000,000 persons   But one can find repeated records of the condition in two or more members of a family, hence the constant association between the disease and the same family can be due to one thing only, namely, heredity   Such a condition is pseudohypertrophic muscular dystrophy   Gough has estimated that it occurs about once in every 100,000 persons   Hence the finding of two in the same family affected with this condition, were it dependent upon chance and not heredity, would occur only once in ten billion times   Now we might find one such record since the disease was first recognized, and that one might be the one in ten billion   But when one can show that family after family shows two, three or more affected, when one walks into a hospital and finds, as I did recently, four children with the condition, brother and sister, and two brothers, the two groups being first cousins, then heredity becomes the only explanation   Hence the occurrence of the same defect or disease, if very rare, in just two members of the family, is sufficient to indicate the hereditary nature of the condition, provided of course that it is neither traumatic nor infectious in origin

d Frequency of disease in related persons compared with that in unrelated persons

How can a disease be regarded as hereditary in character, if one cannot follow any of the above methods?   Suppose that one cannot construct a lengthy pedigree, that there is no excess of consanguineous marriages among the parents of the defectives, that among the number of cases reported there are no instances of twins or too few instances of twins for statistical purposes, and that the incidence of the condition in the general population is impossible to obtain from medical records   How can one proceed under such circumstances?

There is a way in which one can gain some idea of the part heredity

plays, it is by comparing the number of times that two unrelated persons in the same family, namely husband and wife, are affected with the condition, with the number of times that parent and child, or children in the family are affected   If the condition be one dependent upon chance alone, not being infectious or traumatic in origin, and if one finds unrelated persons in the same environment affected as frequently as related persons, then the conclusion may be reached that the condition is either non-hereditary, or one which is so universal in the hereditary make-up of the population that all might be expected to show it   If on the other hand, one found that husband and wife were affected far less frequently than were related persons, one could conclude with a large degree of justification that heredity and not chance was the explanation of two related persons showing the defect   If parent and child were affected more frequently than children only in the family, it would indicate that the majority of cases were probably dependent upon dominant factors, whereas if children only in the family were affected more frequently, it would indicate dependence upon recessive factors   If males are affected in far greater numbers than females, (provided that the condition is one which does not occur in the male reproductive system, or is not dependent upon secondary sex characters), it indicates in all probability dependence upon sex-linked recessive factors

An illustration will be given here of the results which one obtains from investigations   In 117 families in which there were at least two persons affected with Friedreich's ataxia, there were none in which husband and wife were affected, 32 in which parent and children were diseased, and 85 in which children only had the condition   Thus infection, or environment are not etiological factors, and the hereditary factors responsible are in all probability wholly or in part recessive   If the latter is true, and if the series is large enough, one would expect to find consanguineous marriages with undue frequency   There were in the series two cases where the parents were first cousins,—an incidence about nine times the normal   There were two cases of twins affected, once both boys, said to be identical, once, both girls, one affected with the ataxia, the other apparently without the ataxia, but insane

In polydactyly, from a series of cases collected at random, there

were 81 instances in which parent and child were affected, 22 in which children only showed six fingers   In the latter instances, although the parents were free, there were near relatives affected, and the question here arises, had X-ray pictures been taken of the hands of those apparently free but transmitting the defect, would they have been found to show bifid metacarpals, thus indicating the beginning of the condition, or would they have been wholly normal?

Most of the cases of the apparently recessive type of transmission were from a family in which there had been much inbreeding, so that it was possible to explain the pedigree on the basis that the condition was here due to recessive factors   In this series only twice in the 103 families listed were husband and wife affected   The excess of instances in which the condition occurred in those related by blood of course indicates the hereditary nature of the defect

One more illustration will be given, and in this we will choose a condition which is far more frequent, in fact, has been said to be sufficiently frequent in the population to cause statisticians to state that its occurrence in two members of the family can be expected on the basis of chance   Let us look at a series of carcinoma of the gastrointestinal tract   In 71 families, it was found that, 51 times parent and child had the same type of tumor, 20 times children in the family were affected, and both parents free, and 7 times husband and wife were affected with the same type of tumor   Thus unrelated persons were affected in 10 per cent of the series, and related persons in 100 per cent, for in all instances in which husband and wife were affected, children were also affected   With those related showing the same condition ten times as frequently as those not related, there seems to be little doubt that heredity plays a very important rôle in the etiology of cancer

Inasmuch as parent and child were affected in 71 per cent of the cases, and children in the family only, in 29 per cent of the cases, it would appear as if dominant factors were responsible, either wholly, or in combination with other factors, recessive or dominant in character   The fact that children do show gastric carcinoma in over a quarter of the cases, when their parents were not affected, even although some of them lived to the cancer age, would again suggest that recessive factors might be involved   It has been suggested that

entodermal tumors in particular, perhaps most tumors, have two sets of factors responsible for their formation, one a recessive group, located in the sex chromosome, one a dominant located in an autosome   The latter would determine site of cancer growth   This explanation of recessive sex-linkage would account for the fact that tumors common to both sexes are twice as frequent in the male as in the female, a fact brought out in a study on sex-incidence of entodermal tumors by Macklin (8)

If one makes out a table of all possible matings, considering entodermal tumors to be due to multiple factors, one sex-linked and recessive, the other dominant and located in the autosomes, and if then one chooses all those matings in which two at least in the family could be affected, one finds that in 10 5 per cent of the instances husband and wife will be affected, merely through random matings This is exactly the percentage found in the series of gastric carcinoma referred to above   Parent and child would be affected in 62 5 per cent of the cases, and children only in 37 5 per cent of the cases   These figures are not in such exact agreement with the 71 and 29 per cent actually found, as is the 10 5 per cent just referred to   It is nevertheless significant that they are in the proper order, that is with *parent and child* incidence far in excess of *children only* incidence   Although this method does not give the beautiful precision that one gets from experimental matings, it does lend very valuable aid in ascertaining whether or not a condition is hereditary or merely environmental in its etiology

The other more elaborate methods dealing with proofs of heredity will be found in mathematical treatises   They are usually not available to the physician who is not trained sufficiently in statistical methods to use them as ready tools   They can be found by reference to books dealing with this aspect of the subject (5)

9 EMBRYOLOGICAL CONCEPTS OF HEREDITARY FORCES

Having reviewed the essentials of the science of genetics, and the pitfalls which have stood between the medical profession and a full understanding of these fundamentals, and having briefly discussed the simple methods by which the observer of human inheritance can arrive at scientifically sound conclusions without the aid of experi-

mental matings, we will discuss the embryological conceptions which brings us to a realization that all defects of structure or function which are not brought about by outside forces, mechanical, chemical or bacterial, must be hereditary in origin

a Hereditary forces making for normal development

Let us consider the development of the ovum from the time that it begins its process of maturation in preparation for the great event of fertilization   We know that the ova of some species undergo the reduction division in the stage between primary and secondary oocyte, while others undergo this division between the secondary oocyte and the mature ovum   In some forms the allelomorphic mates come together in a union side by side, in others the union is end to end These mechanisms, by which the process of heredity is made possible, are themselves hereditary, and are regulated by genes within the chromosomes   The whole process of development must be conceived to be under the influence of certain determining factors which regulate the time of appearance of individual organs, their rapidity of growth, their regression later on when not needed   These factors must be bound up in the protoplasm of the egg and sperm which unite to form the individual, and hence are inherited   The ovum of the hen always develops into a chick, the ovum of the human organism always develops into a human baby   The chick develops its membranes at about the 20 somite stage, the human ovum develops its membranes before there is any evidence of the embryo itself   The chick develops its mesoderm after the formation of the primitive streak, the human ovum has mesoderm before there is any hint of the primitive streak present   These factors are constant for the two forms, they are inherited characteristics

The same is true of almost every structure in the embryo   Its development, relative to the stage of development of every other structure in the embryo, is peculiar to the species, and marks it off from other species   These developmental relationships, constant for the species, differing from the developmental relationships of other species, must have come to the individual in the egg and sperm, and must be hereditary

b Possible factors adversely influencing development

Having established the fact that normal development depends upon inherited factors, it is obvious that if some structure fails to develop correctly it can be due only to two causes, (1) some outside influence preventing the structure from developing normally, or (2) the lack of the hereditary determiners for normal development or their suppression by the presence of determiners for abnormal development. For eggs that develop outside the maternal organism, environmental influences could readily be postulated, and indeed, experimentally, they have been shown to alter the development of eggs toward the abnormal. For forms developing within the uterus, however, there can be no alteration in the environment except in three possible ways. Moisture remains constant. There may be fluctuations in the (1) temperature, (2) the oxygen content and (3) the chemical constituents of the mother's blood.

1 Alterations in temperature The temperature can vary only to a slight extent, great variation means the death of the maternal organism. It may not have varied at all in the pregnancies which have produced an abnormal infant. It may have varied in a pregnancy which produced two infants, one abnormal, the other normal. Variation in temperature cannot therefore be looked upon as productive of abnormalities in the human being, although it can be made to produce abnormal forms experimentally.

2 Abnormal chemicals in mother's blood The same is true of chemical constituents of the mother's blood. Although we cannot say with such assurance that these have not been altered during a pregnancy which results in an abnormal child, because we have not tested the blood during the pregnancy, we can say, in those instances in which twins are born, one abnormal, the other normal, that had there been any alteration in the chemistry of the maternal blood stream, and were such alterations productive of abnormalities, then both fetuses should have been abnormal, inasmuch as both were subjected to the same chemical changes. That they were not both abnormal is adequate proof that in those cases at least, chemical alterations in the maternal blood were not the etiological factor. If they were not the cause in the case of abnormality in one child of twins, the

evidence is good that they are not the cause of abnormalities when one child only is born at a time

3 Deficient oxygen supply Oxygen supply might conceivably be at fault, for even in the case of twins, there might be placental infarcts at the points at which the villi of the abnormal fetus were attached, and none at the site of attachment of the villi of the normal fetus Thus there might be a localized diminution of oxygen or of normal food supply Such a diminution might conceivably alter the development of the organs which were being laid down at the time the oxygen content was diminished Stockard (9) has shown that the tissues which are developing most rapidly at the time the growth is slowed by lowering the oxygen supply are the ones which develop abnormally We might then presuppose a diminished oxygen supply as the factor which causes abnormal development not only in the case of one of twins being affected, but also in the sporadic isolated instances, were it not for two objections which we will now take up

Objections to these as explanation of malformations The first objection is that placental infarcts which might cause a diminution in oxygen supply to one fetus, and not to another, are found in small size in all placentae, and as large as one centimeter or more in more than three-fifths of all placentae If sufficiently large, they cause the death, not the malformation of the infant There is no mention of their being evident to any peculiar degree in the placentae of abnormal fetuses

The second objection is based upon the following facts Stockard has shown that the critical moments in which environmental factors may alter the rate of development of any particular organ are relatively brief, and occur at the time when the anlage of the organ is just beginning to develop The human embryo has practically all its organs well laid down by the time that it is eight weeks old There are many abnormalities which affect the human fetus Therefore the oxygen diminution would have to occur at very specific intervals after fertilization to cause the great variety of malformations which we encounter It would be almost impossible for the oxygen diminution to occur at exactly the same time after fertilization in more than one pregnancy in the same mother

c Malformations are dependent upon heredity

1 Simple combinations of hereditary factors When, therefore, we find occurring in child after child in the same family, a defect localized in one minute group of cells in a single organ, we can conclude that no environmental factor is at the basis of the defect For example, consider polycystic kidneys Here the deficiency is restricted to a small group of cells between the collecting tubules proliferating cephalically, and the secretory Bowman's capsule developing in the nephrogenic cord In the ordinary course of development, these two blind tubules meet, fuse, and the intervening cells deteriorate, leaving an unobstructed passage from the regions of secretion to the exterior This always takes place in normal development, and there must be a factor which determines this fusion and disappearance of the fused ends of the tubules We can hardly conceive of an environmental condition, such as reduced oxygen supply acting upon such a small and select group of cells as those lying between the secretory and excretory regions of the embryonic kidney, in even one pregnancy, and it is beyond the bounds of imagination to conceive of it acting upon the same tissue through generation after generation The same is true of atresia of the bile duct, which occurs in pregnancy after pregnancy in the same mother If there be an inherited factor guiding the disappearance of the cells in the normal kidney or normal bile duct (and we must admit that there is), it is not difficult to understand how there might be an inherited factor preventing their disappearance, thus causing polycystic kidneys or atresia of the bile duct in many children in the same family

So we might go through the whole realm of malformations and defects of the new born, which are usually not looked upon as inherited, and find that in some families there have been more than one child affected with the condition We can only conclude that it is hereditary More than this, we find records of identical twins both suffering from the same defect Rarely do we find fraternal or heterozygous twins suffering from the same congenital defect, especially if that defect be a rare one These observations emphasize the hereditary nature of these anomalies, and indicate that the instances in which the defect occurs in but one child in the family

are inherited, but have not been passed on to more than one in the family. There are two reasons why only one child in a family may be affected   They are (1) the family may be so small as not to give opportunity for the defect to appear in more than one offspring, even when the defect is one which might occur in as many as one in four, and (2) the combination of factors necessary for the production of the defect is so complex that not more than once in a hundred or five hundred times will that combination be apt to occur

The latter set of conditions can be well illustrated by referring to a card game   What are the chances that a player will receive the ace, king, queen and jack of hearts?   The chances for a player receiving any given card, the ace of hearts in this case, is one in four   They are also one in four that he will receive the king of hearts   They are therefore one in sixteen that he will receive the ace and the king at the same time   They are one in sixty-four that he will receive the queen in addition to the ace and king, and that he will receive all four face cards in the suit of hearts, the chances are but one in 256.

2. Complex combinations of hereditary factors   Now let us suppose that the defect in question is one which is dependent upon four different genes in four different chromosomes, and that the chances of each one of these genes being present in the germ cells in the proper combination was one in four   Then only once in every 256 fertilizations of egg by sperm would this particular combination be made   Suppose that it were made once in the family, the chances would be very great against its being made again in that family   Therefore the defect would appear as an isolated one and its inheritance would not be suspected.   Various theories would be put forth as to its etiology, but heredity would not be one of them   This is what has happened in most of the congenital malformations, and in some of the mental defects which are relatively rare, such as Mongoloid imbecility   Reproductive exhaustion, age of the mother, endocrine dysfunction in the mother, etc , have all been advanced as explanations of the latter   It is in reality an inherited defect of the nervous system which is dependent upon so complex a grouping of factors that it occurs but once in a family in the majority of cases (10)

Amaurotic idiocy, on the other hand, is sufficiently simple in the manner of its inheritance that more than one is affected in a family

quite often, hence its hereditary nature has been recognized   Even here, however, there are many families in which only one has inherited the defect

Tables 3 and 4 are given showing how amaurotic idiocy (which we will represent as present when the mature germ cell has the combination of factors *aa*), and Mongolian imbecility (which we will represent as present only when the mature germ cell contains four sets of factors, *aa, bb, cc, dd*), differ in their opportunities to appear in more than one child to a family

In these two tables the possible combinations of *chromosomes* in the egg and the sperm are shown in the column across the top and the column down the left side of the page   The combinations of egg and sperm are shown in the rest of the table   In table 4 the sixteen different combinations of the four dominant factors A, B, C, D and their

TABLE 3

SPERM	EGG	
	A	a
A	AA	Aa
a	Aa	*aa*

recessive allelomorphs a, b, c, d are shown, as well as the 256 possible combinations of these to produce a fertilized ovum   It will be noted that only once in the 256 squares is the combination *aa bb cc dd* made, namely in the lower right hand square   It will be seen that of the 256 combinations only 81 are capable of being the parents of offspring who have the combination *aa bb cc dd*   When the germ cells of these 81 types mature, they are able, when fusing with an appropriate germ cell, to make the desired combination   The remaining 175 combinations are such that even when the germ cell has matured, and mated with the most desirable germ cell (that is desirable from the standpoint of securing the combination *aa bb cc dd*), the combination is impossible   It will be noted that each of the 81 combinations has at least one recessive factor in each of the four chromosomes, in other words, it has an *a, b, c* and *d*   Where any one of the factors exist in duplicate dominant form, such as AA, it is impossible to get a germ cell containing the requisite recessive *a*

TABLE 4

EGG

SPERM	ABCD	aBCD	AbCD	abCD	ABcD	aBcD	AbcD	abcD	ABCd	aBCd	AbCd	abCd	ABcd	aBcd	Abcd	abcd	(n)
ABCD	AABB CCDD	AaBB CCDD	AABb CCDD	AaBb CCDD	AABB CcDD	AaBB CcDD	AABb CcDD	AaBb CcDD	AABB CCDd	AaBB CCDd	AABb CCDd	AaBb CCDd	AABB CcDd	AaBB CcDd	AABb CcDd	AaBb CcDd	1
aBCD	AaBB CCDD	aaBB CCDD	AaBb CCDD	aaBb CCDD	AaBB CcDD	aaBB CcDD	AaBb CcDD	aaBb CcDD	AaBB CCDd	aaBB CCDd	AaBb CCDd	aaBb CCDd	AaBB CcDd	aaBB CcDd	AaBb CcDd	aaBb CcDd	2
AbCD	AABb CCDD	AaBb CCDD	AAbb CCDD	Aabb CCDD	AABb CcDD	AaBb CcDD	AAbb CcDD	Aabb CcDD	AABb CCDd	AaBb CCDd	AAbb CCDd	Aabb CCDd	AABb CcDd	AaBb CcDd	AAbb CcDd	Aabb CcDd	2
abCD	AaBb CCDD	aaBb CCDD	Aabb CCDD	aabb CCDD	AaBb CcDD	aaBb CcDD	Aabb CcDD	aabb CcDD	AaBb CCDd	aaBb CCDd	Aabb CCDd	aabb CCDd	AaBb CcDd	aaBb CcDd	Aabb CcDd	aabb CcDd	4
ABcD	AABB CcDD	AaBB CcDD	AABb CcDD	AaBb CcDD	AABB ccDD	AaBB ccDD	AABb ccDD	AaBb ccDD	AABB CcDd	AaBB CcDd	AABb CcDd	AaBb CcDd	AABB ccDd	AaBB ccDd	AABb ccDd	AaBb ccDd	2
aBcD	AaBB CcDD	aaBB CcDD	AaBb CcDD	aaBb CcDD	AaBB ccDD	aaBB ccDD	AaBb ccDD	aaBb ccDD	AaBB CcDd	aaBB CcDd	AaBb CcDd	aaBb CcDd	AaBB ccDd	aaBB ccDd	AaBb ccDd	aaBb ccDd	4
AbcD	AABb CcDD	AaBb CcDD	AAbb CcDD	Aabb CcDD	AABb ccDD	AaBb ccDD	AAbb ccDD	Aabb ccDD	AABb CcDd	AaBb CcDd	AAbb CcDd	Aabb CcDd	AABb ccDd	AaBb ccDd	AAbb ccDd	Aabb ccDd	4
abcD	AaBb CcDD	aaBb CcDD	Aabb CcDD	aabb CcDD	AaBb ccDD	aaBb ccDD	Aabb ccDD	aabb ccDD	AaBb CcDd	aaBb CcDd	Aabb CcDd	aabb CcDd	AaBb ccDd	aaBb ccDd	Aabb ccDd	aabb ccDd	8
ABCd	AABB CCDd	AaBB CCDd	AABb CCDd	AaBb CCDd	AABB CcDd	AaBB CcDd	AABb CcDd	AaBb CcDd	AABB CCdd	AaBB CCdd	AABb CCdd	AaBb CCdd	AABB Ccdd	AaBB Ccdd	AABb Ccdd	AaBb Ccdd	2
aBCd	AaBB CCDd	aaBB CCDd	AaBb CCDd	aaBb CCDd	AaBB CcDd	aaBB CcDd	AaBb CcDd	aaBb CcDd	AaBB CCdd	aaBB CCdd	AaBb CCdd	aaBb CCdd	AaBB Ccdd	aaBB Ccdd	AaBb Ccdd	aaBb Ccdd	4
AbCd	AABb CCDd	AaBb CCDd	AAbb CCDd	Aabb CCDd	AABb CcDd	AaBb CcDd	AAbb CcDd	Aabb CcDd	AABb CCdd	AaBb CCdd	AAbb CCdd	Aabb CCdd	AABb Ccdd	AaBb Ccdd	AAbb Ccdd	Aabb Ccdd	4
abCd	AaBb CCDd	aaBb CCDd	Aabb CCDd	aabb CCDd	AaBb CcDd	aaBb CcDd	Aabb CcDd	aabb CcDd	AaBb CCdd	aaBb CCdd	Aabb CCdd	aabb CCdd	AaBb Ccdd	aaBb Ccdd	Aabb Ccdd	aabb Ccdd	8
ABcd	AABB CcDd	AaBB CcDd	AABb CcDd	AaBb CcDd	AABB ccDd	AaBB ccDd	AABb ccDd	AaBb ccDd	AABB Ccdd	AaBB Ccdd	AABb Ccdd	AaBb Ccdd	AABB ccdd	AaBB ccdd	AABb ccdd	AaBb ccdd	4
aBcd	AaBB CcDd	aaBB CcDd	AaBb CcDd	aaBb CcDd	AaBB ccDd	aaBB ccDd	AaBb ccDd	aaBb ccDd	AaBB Ccdd	aaBB Ccdd	AaBb Ccdd	aaBb Ccdd	AaBB ccdd	aaBB ccdd	AaBb ccdd	aaBb ccdd	8
Abcd	AABb CcDd	AaBb CcDd	AAbb CcDd	Aabb CcDd	AABb ccDd	AaBb ccDd	AAbb ccDd	Aabb ccDd	AABb Ccdd	AaBb Ccdd	AAbb Ccdd	Aabb Ccdd	AABb ccdd	AaBb ccdd	AAbb ccdd	Aabb ccdd	8
abcd	AaBb CcDd	aaBb CcDd	Aabb CcDd	aabb CcDd	AaBb ccDd	aaBb ccDd	Aabb ccDd	aabb ccDd	AaBb Ccdd	aaBb Ccdd	Aabb Ccdd	aabb Ccdd	AaBb ccdd	aaBb ccdd	Aabb ccdd	aabb ccdd	16

From the rarity with which Mongoloid imbeciles are found more than one to a family, it has been estimated that at least *five* pairs of recessive factors are involved in the production of *this mental deficiency* (10) The malformations or defects which are found frequently in more than one child in a family are those which are dependent upon a relatively few recessive factors, while those which are seldom found in more than one child in a family are dependent upon complex groupings of factors It is never safe to assume, however, that because a condition is rarely found in two children in a family, that it cannot occur in two Thus the physician who assured his patient that, although she had had one child born with atresia of the ileum, colon and rectum, as well as other malformations, she could not have another such, was deeply chagrined when the second child was born with exactly the same series of defects The same was true of the physician who assured a mother that her other children would not show the same defect that characterized her first offspring, namely, three deformed fingers on each hand Her second baby had hands exactly like the first The parents were uncle and niece in this case

It is not correct to assume that rare malformations will not affect two or more children in the family, nor is it correct to assure the parents that a defect found in the first child will not be repeated in subsequent offspring, because the first-born is more susceptible to defective development These conditions are inherited, and as such are apt to occur again, once they have shown themselves, and are just as apt to occur in the second or the third child in the family as they are in the first (11, 12)

d Summary

Let us sum up briefly then the status of heredity as an etiological factor in causing developmental defects We know that there are hereditary determiners for the normal process of development It is inconceivable that an environmental factor, operating through a short and specific space of time could produce in more than one child in a family and sometimes through several generations, exactly the same developmental anomaly The presence of the same malformation in both identical twins if one of them has it, and the rare occurrence of the same malformation in both fraternal twins, if one of them

has it, also strengthens the idea that heredity and not environment is the causative agent in their production, for fraternal twins and identical twins are alike in that they have the same prenatal influence for each member of the pair, but differ in that there is a similar heredity for each member of the pair in the case of identical twins, and a dissimilar heredity for each member of the pair in the case of fraternal twins Developmental defects, like developmental normalities, are hereditary.

10 HEREDITARY DISEASES, OTHER THAN MALFORMATIONS

Now let us turn to diseases and to alterations in function of the organs that are not dependent upon congenital defects   They are not infectious in origin, nor are they due to trauma, they are dependent upon poor material used in the construction of the individual   The patient may have no obvious structural defects, but he may be made of poor materials   Thus the man who dies of apoplexy has poor tubing or vital rubber, as Sir William Osler expressed it   The man who dies of nephritis has kidneys that are not built of material that lasts as long as the rest of his body   The patient with Friedreich's ataxia, or lenticular degeneration or amaurotic idiocy has poor material in his nervous system   Examination of the tissues before the disease began might show no structural alteration, the variation from normal might be a chemical one which revealed itself through function, not morphology.

When this hereditary inferiority involves any tissues other than the nervous, the disease becomes more severe as the degenerative process spreads   Thus the diabetes may be mild if little pancreatic tissue is involved in the change, or severe if more pancreas is degenerating   The nephritis is mild or severe as little or much of the kidney is involved   But in the case of the nervous system, this is not true   Just as soon as the disease process spreads, it alters the entire picture, and we have another disease entity, as far as clinical nomenclature is concerned

If the deterioration has been localized in the posterior columns, the main symptoms are sensory disturbances   Let the process shift ever so slightly laterally as to include the lateral columns, and motor involvement begins, and an entirely new train of symptoms, with a

new clinical designation, is recognized If the dystrophy affects the lower limbs it is Erb's juvenile dystrophy, but if it attacks the face and neck, it is the Landouzy-Dejerine dystrophy If the paralysis has been of a flaccid type, a slight shift in the degenerative process may change it into a spastic type Thus we have many different names for what is after all the same disease, an abiotrophy of the nervous system It is merely because the symptoms change so radically as different parts of the nervous system are involved that we have given them so many different names

It is not be wondered at that, under the circumstances, so many of the nervous diseases remain unclassified, because they partake of the nature of more than one disease They do not conform to the classical text-book description of any one On the other hand, it is to be wondered at that with such opportunity for variation there should be such constancy of symptoms, both as to the sequence of onset, time of onset, and extent of involvement in members of a family Thus one finds that although the range of age of onset of Friedreich's ataxia in different families may be a matter of twenty years or more, if one member of a family develops it at 10, the others who show it also develop it at about the same age, while if the first member did not develop the disease until 25, the others develop theirs at about that age Literally hundreds of instances of such occurrences might be given, the examples being drawn not only from diseases of the nervous system, but from all inherited disorders Particularly striking is the tendency for identical twins to develop the same disease at about the same age, also of significance is the fact that the severity of the disease is apt to be about the same Thus two sets of identical twins with diabetes showed almost identical blood sugar readings for the two members of the pair

The second way in which one notes the hereditary tendency exhibited by these diseases is in the sequence of onset of symptoms Thus in one family, it will be the scoliosis which first attracts the attention of the family to the fact that the disease is beginning in one of their members, in another family it will be the ataxia of the feet or hands which is the first symptom noted, while in a third family it will be the deformity of the feet which is the first evidence of the malady

This similarity of time of onset, sequence of symptoms and extent

has it, also strengthens the idea that heredity and not environment is the causative agent in their production, for fraternal twins and identical twins are alike in that they have the same prenatal influence for each member of the pair, but differ in that there is a similar heredity for each member of the pair in the case of identical twins, and a dissimilar heredity for each member of the pair in the case of fraternal twins   Developmental defects, like developmental normalities, are hereditary

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If the deterioration has been localized in the posterior columns, the main symptoms are sensory disturbances   Let the process shift ever so slightly laterally as to include the lateral columns, and motor involvement begins, and an entirely new train of symptoms, with a

new clinical designation, is recognized   If the dystrophy affects the lower limbs it is Erb's juvenile dystrophy, but if it attacks the face and neck, it is the Landouzy-Dejerine dystrophy   If the paralysis has been of a flaccid type, a slight shift in the degenerative process may change it into a spastic type   Thus we have many different names for what is after all the same disease, an abiotrophy of the nervous system   It is merely because the symptoms change so radically as different parts of the nervous system are involved that we have given them so many different names

It is not be wondered at that, under the circumstances, so many of the nervous diseases remain unclassified, because they partake of the nature of more than one disease   They do not conform to the classical text-book description of any one   On the other hand, it is to be wondered at that with such opportunity for variation there should be such constancy of symptoms, both as to the sequence of onset, time of onset, and extent of involvement in members of a family   Thus one finds that although the range of age of onset of Friedreich's ataxia in different families may be a matter of twenty years or more, if one member of a family develops it at 10, the others who show it also develop it at about the same age, while if the first member did not develop the disease until 25, the others develop theirs at about that age   Literally hundreds of instances of such occurrences might be given, the examples being drawn not only from diseases of the nervous system, but from all inherited disorders   Particularly striking is the tendency for identical twins to develop the same disease at about the same age, also of significance is the fact that the severity of the disease is apt to be about the same   Thus two sets of identical twins with diabetes showed almost identical blood sugar readings for the two members of the pair

The second way in which one notes the hereditary tendency exhibited by these diseases is in the sequence of onset of symptoms Thus in one family, it will be the scoliosis which first attracts the attention of the family to the fact that the disease is beginning in one of their members, in another family it will be the ataxia of the feet or hands which is the first symptom noted, while in a third family it will be the deformity of the feet which is the first evidence of the malady

This similarity of time of onset, sequence of symptoms and extent

of symptoms in members of the same family, observed in diseases involving the nervous system, speaks very strongly for the hereditary nature of the condition   Because of the spectacular nature of nervous disease, obvious even to the laity, then hereditary nature has been recognized if they affect more than one generation   If a given nervous disease tends to affect children in a family, in which there has been no previous history of it, it is called familial   If it has occurred but seldom as a familial disease, the medical profession has not regarded it as hereditary, although if it had occurred frequently enough, it is so regarded, as for example, amaurotic idiocy

a   Frequency of occurrence of hereditary diseases

Although all of the above facts regarding the importance of heredity in disease might be unquestioned by the average person, he might still be of the opinion that heredity was of little importance as an etiological factor in disease as encountered by the physician   Looking over the table of diseases which is appended, he might feel that most of them were so rare that he had never seen a case of them, and some of them so rare that he had never even heard of them   Therefore, even if these diseases were inherited, heredity as such was of no significance in the average practitioner's practice   This idea is a mistaken one as we shall see shortly

In a recent issue of the Metropolitan Life Insurance Company Bulletin, it was stated that the only six diseases which were not showing a decrease in the death rate, were cancer, diabetes, nephritis, arterio-sclerosis, cerebral hemorrhage and influenza   It will be noted that the first five include many examples of constitutional disorders, in addition to those which are infectious in origin, in other words, an appreciable proportion of these diseases are hereditary.   As we decrease the number of deaths from infectious diseases, we naturally increase those from hereditary disorders   Heredity then becomes a very important factor in disease, and its importance increases as the years pass   Even now, hereditary disorders cause about ten per cent of the deaths in Canada, and if we include tuberculosis which although not inherited in the strict sense of the term, nevertheless depends upon an inherited susceptibility, the percentage of deaths due to hereditary diseases rises to over 20.

11 HEREDITY OF TUMORS

a Fallacies of certain statistical methods in this study

Because most of the diseases which are inherited are rare, we shall not mention them further than to list them in the table of inherited conditions But with cancer, the proof of its inheritance will be taken up a little more in detail, because of its importance from a preventive standpoint Much of the argument applied to the proof of inheritance in cancer would be equally applicable to all other diseases which are sufficiently rare not to be found uniformly through the population

Is it recognized widely that cancer is inherited? The answer to that is rather emphatically in the negative It is true that the geneticists have recognized its hereditary nature in mice, but due to their disagreement upon the mode of its transmission, much of the world has ignored the point upon which they agree, namely that it is inherited Moreover, they have been working with mice, and although the medical profession will believe their proof for mice, they contend that mice are not men, and the argument cannot be transferred to the human being Now if evolution means anything at all, it means that if cancer is inherited in mice, it is inherited in other mammals, at least, in those who show it The geneticists, although agreeing about the hereditary nature of cancer in mice, and recognizing the evolutionary argument, nevertheless are not convinced that there is *proof* of its hereditary nature in man They insist that there should be long pedigrees of incontestable data upon which to base conclusions This requirement cannot of course be fulfilled, because the assigned cause of death may not have been the actual cause of death, unless an autopsy was performed

The second class of persons who have failed to appreciate its hereditary nature are the statisticians They have done perhaps more than any other group to obstruct the progress of truth in this instance They have argued thus "One in every eight persons dies of cancer Therefore it is almost inevitable that one will find many families in which more than one person will have died of cancer To attribute this to heredity and not chance is false reasoning " They have also attacked the problem in another way They have investigated the relatives of those dying of cancer, and the relatives of those not dying

of cancer, and have found approximately the same percentage of cancer cases in both sets of relatives, they therefore conclude that cancer is not inherited

We will briefly discuss these fallacies, and show that cancer is inherited   Although one in eight persons die of cancer, one finds in investigating family histories that it is a specific type of cancer that the family is showing   Thus in one family it is cancer of the breast, in another it is of the rectum, while in another it is glioma of the retina Moreover, the members of the family tend to die of their tumor at approximately the same age, although that age might be far removed from the average age of death from that disease   For example, the average age of death from carcinoma of the breast is between 50 and 55   Yet in one family, the mother and her two daughters died of this condition at 70, 74 and 76   In another family, the mother and her three daughters died of it before they were 22   Now although one in eight dies of cancer, not one in eight dies of carcinoma of the breast As a matter of fact, about one in 10,000 women die of carcinoma of the breast before they have reached the age of 22.   Therefore, if this disease at this age were due to chance, not to heredity, we would expect to find this condition occurring in four women of the family but once in 10,000,000,000,000,000 women   If heredity is the explanation, then one would expect others in the family to show a condition, once it has appeared   If chance is the explanation, then it is almost impossible for it to appear in other members of the family, when it has affected one

Or suppose we consider the family in which a father and two of his three sons had carcinoma of the breast   That condition was just one and a half million times as frequent in the males of that family as it is in the males of the general population of the same age   Here one does not need a long pedigree to assure one of its hereditary nature, just three in a family is enough

The statisticians then have made their mistake in considering cancer as if it were one disease, instead of many.   They have investigated cancer of all kinds instead of limiting themselves to one kind.   It would be just as sensible for us to endeavor to find how many cases of scarlet fever had developed from being in contact with a smallpox case   When we discovered none, we would say that smallpox was

not a contagious disease   If we find how many cases of smallpox have developed from contact with smallpox, we will change our ideas as to the contagiousness of smallpox

When the family history is investigated for the same type of tumor, one finds that it is much more frequent in the ancestors of those with that tumor, than in the ancestors of those who do not have that type of tumor   Thus if the patient has cancer of the breast, cancer of the breast will be found more frequently in her ancestors than will cancer of the breast be found in the ancestors of a patient with cancer of the uterus   Also cancer of the uterus will be found far more frequently in the ancestors of a patient with cancer of the uterus than it will in the ancestors of the patient with cancer of the breast   In other words, the descendants of a person with a tumor are far more apt to have that same type of tumor than they are to have any other type

Now at this point, the objectors to this idea will point out that frequently the type of tumor does differ   Thus the father will die of gastric carcinoma, the son of lip cancer   This is quite true, but it does not say that either of these types of tumor are not inherited   It merely means that in the family in question, there existed genes for more than one type of tumor   Thus the mother may have had the gene for lip cancer, which she did not develop herself, and which she passed on to her son, or the father may have had two genes, one for cancer of the lip, the other for cancer of the stomach   The age at which the latter develops is ten or more years sooner, on the average, than the age at which lip cancer develops   Therefore the father might have died before he had a chance to show lip cancer   The son who inherited the gene for lip but not the gene for stomach cancer was thus able to live until his lip cancer grew   Although there are numerous instances in which members of a family die of different tumors, there are more cases in which the members of the family die of the same tumor

Let us view the statistician's approach to this question from the other angle   It was stated that one of the favorite modes of determining the inheritability of cancer or any other disease, was to ascertain the percentage of affected ancestors of the patient, and of a control population who did not have the disease   The statistician has found that there is the same percentage of ancestors dying of

cancer when the patient did not die of cancer, as when he did. There-
fore he has concluded that cancer is not inherited   But before we
accept this conclusion, let us examine the data on which it is based
Many of these studies are made on life insurance data.   The vast
majority of life insurance policy holders are men   Thirty-five per
per cent of all cancer occurs in the breast, ovary and uterus, organs
which men do not possess   Therefore many men who have inherited
the genes for these types of tumors, cannot develop them, and so will be
listed as non-cancer cases giving a history of cancer   In order to have
such conclusions valid, they should deal either with a representative
population, or with tumors that are common to both sexes, and which
can therefore appear in the group of persons under investigation
Until such studies are more accurately controlled, they must be
discounted

Having shown that the geneticist and the statistician are not in
agreement with the idea that cancer is inherited, we will now turn to
the third class of persons who are not wholly convinced as to the
hereditary nature of this disease   This group is composed of the
majority of physicians   Why do they not believe that cancer is in-
herited?   There are several reasons   The first is that cancer often
occurs in persons who say there is no other case in the family   The
physician not appreciating the recessive mode of inheritance, therefore
says cancer is not inherited   The second is that they are enamoured
of the idea that trauma or chronic irritation is the cause   They read
of experiments where rabbits have been painted with tar and develop
skin cancer, or where gastric cancer is produced in rats by feeding
them cockroaches, or where liver cancer is found in rats whose livers
contain parasites   They therefore assume that all cancer must be
due to irritation   One might as well assume that, because one can
produce diabetes by removing the pancreas, all diabetics have had
their pancreas removed or have never had any

Again, physicians find that 95 per cent of cervical carcinoma develops
in married women   Therefore they assume that the trauma received
at childbirth is responsible for cervical carcinoma   Some of them even
go so far as to state that this type of carcinoma can be eliminated by
the careful repair of all lacerations following childbirth   But what
these advocates of the chronic irritation theory forget is this over 90

per cent of all women are married before the age at which cervical carcinoma develops, therefore the state of marriage does not seem to have such a striking effect upon the production of cervical carcinoma as the first figures would suggest This estimate of the number of women over 40 who have been married was made from Canadian data, obtained from the 1921 Census

b Chronic irritation over-emphasized

Chronic irritation undoubtedly plays a role in causing cancer, but its rôle has been over emphasized It has been shown that not all rabbits whose skin is painted develop skin cancer, not all chimney sweepers develop scrotal cancer, not all smokers develop lip cancer Chronic irritation only succeeds in producing cancer where there is an inherited susceptibility It acts as an accelerator, speeding up a reaction which was destined to occur if the individual lived long enough The reaction occurs earlier than it would have occurred without the stimulus of the irritation My opponents might easily object here that I am assuming this rôle for chronic irritation, which cannot be proved They say that we do not know when the tumor would have developed without the trauma, or indeed, if it would have developed at all

At this point, identical twins with tumors, furnish excellent proof There is a record of identical twins (16), one of whom developed sarcoma of the right testis at the age of 26 He had had an injury to the right testis a few months before the appearance of the tumor His twin brother had never received any injury to his right testis, but at the age of 31, he also developed a sarcoma of the right testis Both brothers were destined to develop this tumor at about the age of 31, but the injury speeded up the reaction by about 5 years Had there been no twin as a control in this case, the man who developed a sarcoma following injury would have been listed as one more example of tumor following trauma

The same uncritical statements are made with respect to many observations of the relation between chronic irritation and cancer Thus one finds it stated that the reason why lip and mouth cancer are found much more frequently among men than among women, is because men smoke, and women do not, or at least did not to any extent

forty years ago, which would bring them to the lip cancer age about now   Now from Canadian statistics of 1932, it is seen that only one in every 4635 men over 40 died of cancer of the mouth and lip in that year.   Yet certainly there are far more men who are smokers than one in every 4635   No doubt, irritation does speed up the abnormal reaction in men who smoke pipes, and who have an inherited susceptibility for lip cancer   One of the main reasons why women do not develop lip cancer is this, its onset is relatively late in life, and the vast majority of women who die of cancer have succumbed to uterine or breast cancer at an age 15 to 20 years younger than the average age for death from lip cancer.   In other words, most women do not live long enough to die of lip cancer if they have inherited a factor for cancer at all   For fuller references to instances of inheritance in tumors, see Macklin's papers on this subject (17, 18, 31, 32)

Hence, when we view the problem of the etiology of cancer from the standpoint of the geneticist, the statistician and the physician, we find that cancer is inherited   It is dependent upon factors, some of which are recessive in many if not in all instances, and hence may appear in persons in whose family there is no history of it   There is a striking tendency for the members of a family to develop the same type of tumor, in the same organ at about the same age   The frequency with which this specificity of tumor type is found in the same family suggests the presence of dominant factors as well, especially regulating the site and type of tumor   It has been suggested that there are two sets of factors connected with tumor formation, a pair of recessive factors responsible for abnormal tissue proliferation, and a dominant pair responsible for the organ in which this proliferation takes place   Macklin has suggested that the recessive pair are located in the sex chromosome (8)   If chance is responsible for tumor formation, that is, if it is dependent upon some factor other than heredity, it would be extremely seldom that more than one person in a family should show the same type of tumor, in the same organ and at the same age   Unrelated persons in the family such as husband and wife, should show the same type of tumor with the same frequency that related persons, such as parent and child, a brother and sister, are affected   If heredity is responsible for tumor formation, then it is the natural thing to find a second member of the family showing the same type of tumor

as has the first one   Although irritation is no doubt a factor, and in some cases a potent factor, in causing tumors to develop, it operates only where there is an inherited susceptibility, or potentiality for tumor formation   Sometimes the hereditary factor may be so weak that the external stimulus must be very strong, and hence comes to the fore, in others the hereditary factors are so powerful that no obvious external stimulus is needed (19)

Much of this argument of a statistical nature can be applied to other rare diseases   Thus one can show that muscular dystrophy or Friedreich's ataxia are to be found once in so many times in the population   Therefore two members of a family would be affected with the same condition once in that number squared were the condition dependent upon environmental factors other than contagion   When one finds two members of a family affected time after time, it is impossible for such defects to be merely a matter of chance   Heredity becomes the only possible explanation

12 INHERITANCE OF MENTAL DISEASE

Although diabetes, cancer and some forms of cardio-vascular diseases are hereditary, and as such might be thought to offer opportunities for prevention through selective mating, they are also combined in numerous cases, with other excellent hereditary traits, so that their deleterious effects are more than offset by the latter   When we come to the field of mental disease we meet with a very different situation   Although certain of the psychoses do no doubt occur in persons with other admirable traits, many of the diseases of the mental type occur at an early age, and so alter the mentality as well as the personality of the patient as to render him useless to himself, and a distinct burden to the community, which in large measure supports these mental patients

a Epilepsy

There has been a great deal of altercation concerning the inheritance of epilepsy   Some workers affirm that epilepsy is found in the ascendants of the non-epileptic as often as it found in the ascendants of the epileptic   Others affirm that idiopathic epilepsy is definitely hereditary   It must be remembered that epilepsy is a symptom, not

for it does happen that occasionally normal parents have a feeble-minded child   When both parents are feeble-minded, normal children are said not to occur   If they are found as offspring when both parents are feeble-minded, it is said that they are illegitimate children of the feeble-minded mother and a normal father   Feeble-mindedness is found twice as often in males as in females, and for this reason it has been attributed to a sex-linked recessive factor (30)   If this is so, it means that sex linked dominant factors must be responsible for mental efficiency   Other factors than sex-linked ones probably enter into the mental make up of the person, however   This idea is of interest, for if it is correct, it means that although a man inherits part of his mental endowment from his father, he must have an intelligent mother if he is to be intelligent   It may not be sentiment that has been at the basis of the statement that many great men attribute their mental endowment to the intelligence of their mothers

Because of the large families among the feeble-minded (much larger on the average than are the families of the mentally normal), and because of the selection of mates, feeble-minded marrying their like rather than normal persons, the rate of increase among the feeble-minded is far in excess of the rate of increase among the remainder of the population   There are some who question the inheritance factors in this type of mental defect, but a glance at the inmates of the homes for feeble-minded shows that it is not scattered promiscuously through the population, but is, in the majority of instances, definitely segregated in certain families   Those who claim that normal persons often produce feeble-minded offspring should test the intelligence of the so-called normal parents   In many cases defective intelligence would probably be found in them

There are some cases of mental deficiency which are definitely not inherited, which are caused by encephalitis, birth injuries, or toxins of infectious diseases, this group, however, is very much in the minority   Here again research, based on facts, not preconceived theories, is much needed

c   Manic-depressive psychosis

When we invade the realm of the psychoses, where structural alterations are not visible in the nervous system, we enter a field of

intense controversy   The tendency among some modern psychiatrists and psycho-pathologists is to attribute the various psychoses to psychic trauma received in youth, to repressed desires, to submerged complexes, etc   Most of these repressions and submersions center about sex   When they are dragged forth, and the patient gazes at them, recognizing them for what they are, they are supposed to

"Fold their tents like the Arabs, and as silently steal away "

That they do not do so, as evidenced by the large number of psychotic patients still within our institutions, indicates either the inadequacy of this type of psychiatrist as a therapeutist, or the fallacy of his reasoning with respect to the etiology of many of the psychoses.

Much of psychiatry and psycho-pathology needs to be put upon a strictly scientific basis   This has not been universally done up to the present   For example, some psychiatrists, in obtaining the life history of the patient, disinter old buried ideas about sex longing, sex curiosity, repression of these, etc   They at once assume that they have found the cause of the psychosis   If they were following a strictly scientific procedure, they would use normal persons, without a psychosis, as controls   They would find in many of them the same buried complexes, the same repression   They would then conclude that inasmuch as the complexes and repressions were present in both but the psychosis was not, other factors must be responsible for the variation in results observed   They would find that the other factors were to be found in the unstable nervous system, the constitutional make-up of the individual, and that this instability, this constitution was inherited just as definitely as poor material in the blood vessels is inherited   They would recognize that the environmental situations are merely the outward and apparent cause, the essential factor was the inherited nervous instability   If the hereditary nervous make-up is sufficiently good, no amount of external stimuli can produce a real psychosis   If the hereditary make-up be sufficiently poor, it is more than probable that no amount of environmental adjustment will guarantee mental stability   Although the endeavors of these enthusiasts are to be commended, in that they may lessen the outward strain below the breaking point in some of the patients, they are only

temporary expedients, for the break will occur just as soon as the patients are removed from the protection of an adjusted situation

Hemophilia is inherited, as all physicians agree, but the hemophiliac will not reveal his tendency to bleed if he is kept absolutely free from all type of injury, in other words, in an environment that will not evoke his hereditary response   But normal persons do not need to be wrapped in cotton wool to keep them from bleeding to death, they have a different heredity   A similar state of affairs holds for the psychotic patient, he may not show his tendency to manic-depressive phases of mental illness if the environment is so adjusted that he has no stimulus to produce this illness   Normal persons, however, do not need such a sheltering situation in order to preserve an even mental keel   Where two factors are necessary to produce a result, such as heredity and an environment in which that heredity may express itself, and if one of the factors, such as environment, be practically universal, then one can speak with truth when one ascribes the result as due to heredity, it being the only variable factor in the equation

Paskind (25, 26, 27), has shown that patients with a manic depressive psychosis have a greater percentage of relatives with an outspoken psychosis than have patients who were designated as psychasthenics   Thus he felt that in the realm of mental disease, like tends to produce like   There is no dearth of records of families in which more than one, sometimes many, members have had manic depressive psychosis   There are frequent records of identical twins with it, and in most of these, the age of onset was about the same   In some twins, the cyclic changes occurred at about the same time, although the twins were not together   Such records are most convincing as to the part which heredity plays in the production of the disease   Despite the theories of the psychiatrist, despite the inability of the cytologist to demonstrate any morphological change in the nervous system of these functional psychoses, this alteration of mentality is inherited   It has been said to be dependent upon a unit dominant factor, passing in the direct line of descent from parent to child   In those instances in which this does not occur, one need not feel that proof has been obtained against the hereditary nature of the disease   Other explanations as to the failure of a parent to exhibit it are scientifically sound

d Dementia praecox

All that has been said of manic-depressive psychosis is true of dementia praecox, with the exception that the former is supposed to be due to a dominant factor, and the latter is said to be recessive in its transmission   The same fallacious reasoning as to its etiology has been put forward by some psycho-analysts, and the same objections to their arguments can be advanced   This disease is found in identical twins, and its occurrence at the same age in both is encountered

Since the condition is recessive in its mode of inheritance, one might suppose that it would be difficult for a potential dementia praecox patient to select from the general population a person who had the factor for the same disease, and hence that it would be difficult to find examples of inheritance of this disease, especially from parent to child It appears, however, that there is selective mating in this as well as in other forms of mental abnormality   It has been found that even when the mental illness has not yet developed in either patient, the psychotic tends to select and mate with his own kind (28)   This tendency accentuates the rate at which such persons increase in the general population   Were their matings indiscriminate the percentage of dementia praecox cases would tend to remain constant in the population

This disease is now so prevalent that it is stated that one-fifth of all hospital beds in the United States are filled with dementia praecox patients   It is becoming progressively more frequent, due not so much to greater opportunity for strain in our modern civilization as to the protective care which that civilization affords them, thus giving them a chance to become partially cured and return to society again and produce more potential schizophrenics

Rosanoff's (29) collection of twins with psychoses shows that identical twins are both affected far more frequently than are both fraternal twins, if one member of the twin pair has the disease   This observation again offers proof of the hereditary nature of the condition

e Huntington's chorea

Huntington's chorea is one type of insanity which is attributed to heredity by almost all workers   This is due no doubt to two causes

One is that it is dependent upon dominant factors, so that its descent from parent to child is easily traced, and its heredity is thus made obvious   The second is that morphological changes can be seen in the nervous system, and hence it is removed from the so-called functional psychoses   From the records I have encountered, longevity is frequently associated with this disease, the patient developing the chorea at about 40, and not dying until 75 or 80 years of age   Most of the cases of Huntington's chorea in the eastern part of the United States and Canada have been said to have descended from three brothers on Long Island (36)   This one family has furnished practically one thousand cases of the disease   Well would it have been for society had they adopted universally the creed of the Persian sage, when he said

> "Better, ah better cancel from the scroll
> Of Universe, one luckless human soul,
>   Than drop by drop enlarge the flood which rolls
> Hoarser than anguish as the ages roll "

13 THE RÔLE OF INHERITANCE IN INFECTIOUS DISEASES

So far we have discussed as hereditary those diseases which had their basis in the constitution of the individual, which were on the whole degenerative in origin, not infectious   It would not be proper to close a discussion of the rôle which inheritance plays in disease, without mentioning the role of inheritance in infectious diseases

Tuberculosis was long regarded as inherited   With the advent of modern bacteriology, it was shown to be due to a pathogenic organism   Inheritance as a contributing factor faded from the minds of the profession   Recent studies have convinced workers that the soil necessary for the development of tuberculosis is due to inheritance   In diseases in which there must be an infectious agent present before the disease can become manifest, the balance of blame to be attached to environment and heredity becomes difficult to determine   Here is where a study of twins is of value   Such a study has been made recently by Diehl and Verschuer (41)   Some of their conclusions drawn from 127 pairs of twins, 45 of which were identical, 82 of which were fraternal, will be given here   There were seven pairs of twins where both members had had a common exposure, but where only

one twin from the pair had developed the disease   Six of these seven pairs were fraternal twins, one pair was identical   Thus where the response was different, fraternal twins, with a differing heredity, but a similar environment, formed 86 per cent of the group, although only 65 per cent of the entire series was fraternal   This is exactly what we would expect if heredity played an important rôle in the causation of tuberculosis.

There were twelve pairs of twins where each pair had been exposed to a healthful and identical environment   Five pairs had one member of the pair only affected, all five pairs were fraternal twins   Seven pairs had both twins affected, and of these, five pairs or 71 per cent were identical twins, two pairs, or 39 per cent, were fraternal   Here again when environment was similar and response was different, the fraternal twins made up the entire series, when environment was the same, and response was identical, identical twins formed twice as large a group as they should, on the basis of expectation   Again, this emphasizes the rôle of inheritance

Twenty-five per cent of the fraternal twins showed both members affected with tuberculosis, but seventy per cent of the identical twins showed both members affected   In the identical twins agreement between the members of each twin pair as to localization and course of the disease was twice as frequent as disagreement   In the fraternal twins, disagreement was fourteen times as common as agreement

All of these facts point to one thing, namely that heredity plays a very important rôle in the production of tuberculosis   We cannot inherit the germ which is the cause primarily of the appearance of the disease, so we must inherit the susceptibility which enables the germ to get a foothold   The authors of this study conclude that about one-fifth of the persons who have inherited the factors for tuberculosis susceptibility do not develop the disease, due to the inheritance of other factors modifying the susceptibility

Evidence that other diseases, known to be infectious in origin, are due to inherited susceptibility is slowly accumulating   Thus with acute rheumatic infections, it has been stated that certain familial characteristics favor the onset of many infections, among them acute rheumatism   Irvine-Jones (42) concludes from her studies that acute rheumatic infection is merely a specialized type of reaction in certain

families caused by a common infective agent, which when encountered by other families, does not cause the rheumatic response   Thus she found that rheumatism was twice as common in families of patients with acute rheumatic infections as it was in families where the patient had some other disease   As two-thirds of the cases occurred when no other person in the family was suffering from the disease, direct contagion could be ruled out as an explanation of this finding

In her cases, there were seven pairs of twins, two of them were identical and five were fraternal   In the identical twins, all four were affected, but in the five pairs of fraternal twins only one member of each pair was affected   This finding again emphasizes the hereditary nature of the rheumatic background

She found that there was no relation between blood grouping and acute rheumatic infections   There was a distinct relation to coloring, however, those who were blond or who had red hair being far more common in the rheumatic families, both as patients and as relatives, than they were in the control population

Exanthematous diseases are said to be far less common among the dark skinned races than they are among the white races   Workers in agricultural stations are finding that chickens are susceptible or immune to certain organisms which they have never encountered before, and which their ancestors have not encountered, so that there can be no talk of transfer of an immunity   These susceptibilities and immunities are hereditary and are transmitted according to Mendelian laws

Every doctor could probably furnish numerous records from his own practice in which families have proved either highly susceptible or immune to infectious diseases   One instance of this I recall   A family A with five children lived next door to a family B, also with five   Three members of family B died of tuberculosis, one died of diphtheria, several had typhoid fever, they all had the infectious diseases of childhood   The children of family A played in the house of family B as much as in their own, but they never developed any symptoms of tuberculosis, nor did they ever have typhoid, although drinking the same water and milk supply that the other family did   Family A had practically nothing but a mild case of measles all around, and one case of mild scarlet fever

one twin from the pair had developed the disease   Six of these seven pairs were fraternal twins, one pair was identical   Thus where the response was different, fraternal twins, with a differing heredity, but a similar environment, formed 86 per cent of the group, although only 65 per cent of the entire series was fraternal   This is exactly what we would expect if heredity played an important rôle in the causation of tuberculosis

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Twenty-five per cent of the fraternal twins showed both members affected with tuberculosis, but seventy per cent of the identical twins showed both members affected   In the identical twins agreement between the members of each twin pair as to localization and course of the disease was twice as frequent as disagreement   In the fraternal twins, disagreement was fourteen times as common as agreement

All of these facts point to one thing, namely that heredity plays a very important rôle in the production of tuberculosis   We cannot inherit the germ which is the cause primarily of the appearance of the disease, so we must inherit the susceptibility which enables the germ to get a foothold   The authors of this study conclude that about one-fifth of the persons who have inherited the factors for tuberculosis susceptibility do not develop the disease, due to the inheritance of other factors modifying the susceptibility.

Evidence that other diseases, known to be infectious in origin, are due to inherited susceptibility is slowly accumulating   Thus with acute rheumatic infections, it has been stated that certain familial characteristics favor the onset of many infections, among them acute rheumatism   Irvine-Jones (42) concludes from her studies that acute rheumatic infection is merely a specialized type of reaction in certain

families caused by a common infective agent, which when encountered by other families, does not cause the rheumatic response   Thus she found that rheumatism was twice as common in families of patients with acute rheumatic infections as it was in families where the patient had some other disease   As two-thirds of the cases occurred when no other person in the family was suffering from the disease, direct contagion could be ruled out as an explanation of this finding

In her cases, there were seven pairs of twins, two of them were identical and five were fraternal   In the identical twins, all four were affected, but in the five pairs of fraternal twins only one member of each pair was affected   This finding again emphasizes the hereditary nature of the rheumatic background

She found that there was no relation between blood grouping and acute rheumatic infections   There was a distinct relation to coloring, however, those who were blond or who had red hair being far more common in the rheumatic families, both as patients and as relatives, than they were in the control population

Exanthematous diseases are said to be far less common among the dark skinned races than they are among the white races   Workers in agricultural stations are finding that chickens are susceptible or immune to certain organisms which they have never encountered before, and which their ancestors have not encountered, so that there can be no talk of transfer of an immunity   These susceptibilities and immunities are hereditary and are transmitted according to Mendelian laws

Every doctor could probably furnish numerous records from his own practice in which families have proved either highly susceptible or immune to infectious diseases   One instance of this I recall   A family A with five children lived next door to a family B, also with five   Three members of family B died of tuberculosis, one died of diphtheria, several had typhoid fever, they all had the infectious diseases of childhood   The children of family A played in the house of family B as much as in their own, but they never developed any symptoms of tuberculosis, nor did they ever have typhoid, although drinking the same water and milk supply that the other family did   Family A had practically nothing but a mild case of measles all around, and one case of mild scarlet fever

The idea of susceptible soil is by no means new, but it is just coming back into prominence in a modified form   It should not be difficult to accept it because we see in our domestic animals a stock which is hereditarily immune to many of the germs to which mankind is susceptible   Not only that idea must be accepted, but the further idea that tissue susceptibility to the same germ may differ in different families   Thus one family may have just tonsillitis, while another develops not only the tonsillitis, but cardiac disease, Sydenham's chorea and joint affections from the same type of germ   We may have to recognize that bacteriologically similar germs may have hereditary predilections for different tissues, so that with varying susceptibilities on the part of man, varying capacities on the part of seemingly similar germs, there is opportunity for widely varying manifestations of disease in mankind

14 PRACTICAL VALUE OF KNOWLEDGE OF INHERITANCE IN DISEASE

All this information is interesting, and can be made of practical value in the profession of medicine, from the diagnostic, therapeutic and preventive aspects   For example, if one member of a family has had gastric carcinoma, it becomes easier to attribute the correct significance to the gastric symptoms of the next member of the family With diagnosis improved, the correct therapy can be more easily applied   The man who has had his gastric carcinoma diagnosed before he is on the autopsy table, has a better chance of getting operative cure while there is still time   But it is in the field of prevention that the greatest value of a knowledge of inheritance in disease lies   There is opportunity afforded of finding the lesion before it becomes carcinomatous, if we know that two brothers have already had gastric carcinoma, and the site of the potential tumor can be excised before it has become malignant, or at least before it has become other than a local lesion

A word must be said here as to the study of human constitution in relation to disease   Recently there has been a renewal of interest in the relation of bodily types, mental types, and disease   Thus we find that certain skeletal conformations, certain body builds, certain metabolic activities are associated with definite disease syndromes   For example the patient with gastric ulcer, or with pernicious anemia, or with hyper-

tension, or with manic depressive psychosis, etc , is supposed to have on the average certain physical structural peculiarities which are commoner to persons with that disease than they are to persons not suffering from that particular disorder   The relation between obesity and diabetes, between obesity and apoplexy, between obesity and cancer have been commented upon   These diseases do not arise because the individual is obese, but the two conditions of obesity and the disease arise because of their association with an inherited constitution that characterizes that patient   Such studies are forcing us more and more to take cognizance of the patient as an individual, rather than as a group of symptoms, a tendency which arose as the profession of medicine became more and more divided into specialties   That tendency is becoming corrected as the patient is regarded as something more than the sum of his ailments

We have tried to visualize the processes which are the physical basis of heredity   We have seen that underlying all development, both normal and abnormal, there is an interaction between the inherited capacities of the individual to develop and the environment in which he is placed   Where the environment is fairly uniform and the response of the individuals is widely different, the stress is naturally and properly laid upon inheritance as the basic cause of the variations in response   Those diseases and malformations which are not due to trauma, mechanical or chemical, to infectious organisms, or to dietary insufficiencies may be regarded as hereditary in nature, having as their ultimate cause some constitutional factor which resulted in a deviation from the normal course of development or from a normal response to an environment   Even those diseases which are infectious or which are due to dietary inadequacies may have as a partial cause inherited factors which make their possessor more susceptible to an environment than are other persons not so hereditarily endowed Environment and heredity, "useless each without the other" become linked inseparably in the physician's mind, and he sees his patient as a product of both; sometimes the environmental factor predominating, as in the realm of infectious diseases, sometimes the hereditary factor so important that environment fades into insignificance   The patient might well paraphrase Ulysses and say,

"All that I have met is a part of me"

Converging streams of germ plasm with their varying potentialities have met to make him what he is, how he reacts to his environment, what disabilities he meets along the way, what form death assumes when finally it removes him from the scene are all largely determined by his heritage

15 LIST OF HEREDITARY DISEASES AND MALFORMATIONS

Achondroplasia Dominant, 12 times, recessive, 5 times One set of twins reported, male affected, female normal No consanguinity in parents

Achylia Dominant for most part

Addison's disease Dominant in one family for 3 generations Recessive mostly, where condition is due to some developmental defect, and not to infectious processes, or to new growths

Alkaptonuria Recessive in twelve families reported Parents related in 6 families, or 50 per cent This incidence is 250 times that found for cousin marriages in the *general population*

Anemias

 Infantile Dominant once, recessive in four cases One pair of identical twins affected

 Sickle cell Dominant in all cases so far reported Occurs almost exclusively in the negro, or those who have an admixture of negro blood

Anencephaly Always recessive in inheritance Eleven families reported where more than one anencephalic fetus was born to a family One set of female identical twins with the condition reported

Ankylosis of finger joints Dominant in 14 families in which it has been reported

Arthritis Dominant through 4 generations in one family, recessive in other families One set of female twins reported with condition Even infectious cases due apparently to inheritance of susceptible soil in which germs may proliferate

Asthma Dominant for most part, but the allergic type not always called forth because patient may not encounter specific protein

Bladder atony Dominant through 3 generations in one family, who had bladder diverticula

Blood groups Triple allelomorphic series, A, B, and O A and B dominant over O, but not over each other Thus there are four groups, (1) OO, (2) AA or AO, (3) BB or BO, and (4) AB

Bones

 Absence of tibia One set of identical female twins reported with this condition Recessive, and rare developmental defect

 Absence of coccyx One family, with two sisters affected, reported Very rare

 Acrocephaly Recessive in almost all cases reported

 Atrophy of femur Dominant through the one family in which it was reported for 6 generations

 Hypertelorism Dominant in the cases reported

 Miscellaneous dystrophies Dominant in 3 families, recessive in 11 families Consanguinity in 4 of the 11 cases, an incidence of consanguinity of 180 times the normal

 Prognathism Dominant usually

 Pigeon breast Dominant in those families where it is not the result of tuberculous disease Two sets of twins, both males, reported with the condition

Cervical ribs Dominant in some cases, apparently recessive in others

Loose joints Dominant mostly

Obelion depressed Dominant in one family through 4 generations

Oxycephaly Recessive for the most part, but dominant in 3 generations in one family

Parietal bones defective Dominant in family in which it was reported One set of female identical twins with both affected, and one set of female twins, with only one affected, reported

Patella subluxation Dominant in practically all the families reported with the condition

Scapula elevated Dominant in the one family reported with it

Radio-ulnar synostosis Dominant in some families, recessive in others

Ankylosed elbow Dominant in one family through 4 generations

Brachydactyly Dominant in most of the families reported, although it is said to be recessive in as many as 23 per cent of the cases.

Branchial fistula Recessive in most cases, although dominant in one family through 4 generations

Club foot Either recessive, or due to multiple factors in most cases In 200 instances, the parents were related in 13 per cent, an incidence 65 times that normally found Two thirds of the cases are in males suggesting that one of the factors at least is a sex linked recessive Four sets of identical twins reported with both members affected

Club hand Very rare One instance of mother and child affected Recessive in inheritance, because most cases arise where both parents are normal

Cranio-cleidodysostosis Dominant in 22 families, recessive in two

Cranio facial dysostosis Dominant in three families, recessive in one

Cystinuria Dominant in some families recessive in others Cousin marriages were very frequent in the largest pedigree reported, by Thin One pair of like-sexed twins with cystinuria are reported

Deaf mutism Recessive in most instances Consanguinity of parents frequent, amounting to 4 5 per cent in one series Nineteen pairs of twins have been reported with deaf mutism

Diabetes insipidus Dominant in most instances reported

Diabetes mellitus Dominant as often as recessive in inheritance although some workers consider it to be always recessive Twenty one pairs of twins reported most of which were identical Consanguinity not noticeably frequent in parents of patients

Dwarfism Due to many different factors causing various types of dwarfism, therefore mode of inheritance varies from dominant to recessive

Edema

  Angioneurotic Dominant in most instances, although mode of transmission varies because onset of disease may be dependent upon extraneous factors, as diet

  Chronic Recessive more often than dominant

Eosinophilia (idiopathic) Dominant in the few families reported

Exostoses Dominant in most instances Cousin marriage in large percentage of cases where recessive inheritance was noted

Foot Due to type of malformation mode of inheritance varies

Gastric ulcer Mostly dominant one pair of identical twins, both affected, reported

Gaucher's disease Recessive Found mostly among those of Jewish extraction No consanguinity noted in 100 cases so far reported

Genitals malformed Imperforate hymen in three sisters, recessive mode of inheritance

  Cryptorchidism Recessive

Goitre Dominant in most instances   Erratic in its mode of distribution, because its appearance dependent upon content of iodine in food, in addition to hereditary susceptibility

Gout Mode of inheritance erratic, because of dependence upon extraneous factors also

Hands malformed Monodactyly, split hand and foot, etc usually dominant, although many of the malformations are recessive in character, showing up in only one to a family   Where two children had ectrodactyly, father and mother were uncle and niece

Harelip Due to recessive or multiple factors

Heart Congenital malformations usually recessive in nature   Two instances reported of identical twins with same congenital malformation of heart

Hematemasis Mostly dominant   Probably due to telangiectasia

Hematuria Mostly dominant   Probably due to telangiectasia

Hemophilia Always sex-linked recessive in cases reported so far

Hemoptysis Mostly dominant   Probably due to telangiectasia

Hemorrhagic diatheses Dominant, and recessive, depending upon the type under consideration

Hermaphroditism Recessive, naturally

Hip dislocation Recessive for most part   One pair of identical twins, both affected

Hydrocephalus Recessive   Consanguinity in 10 per cent of the cases

Hypertension· Dominant usually

Hypospadias Sometimes dominant, mostly recessive

Icterus neonatorum Recessive for the most part   Two sets of like-sexed twins reported with the condition

Intestine malformations Imperforate anus recessive   In 7 families with more than one affected, one had parents related, an incidence of 14 3 per cent, or 70 times the normal   Megacolon mostly recessive   Most other congenital malformations of gut occur but once in a family, and are not regarded as hereditary   Occasionally same defect repeated in a second infant shows that they are hereditary, due to recessive factors, or to multiple ones

Jaundice, acholuric Dominant in most families

Kidneys

   Dwarfism and renal deficiency Recessive

   Hydropic kidneys Recessive

   Polycystic kidneys Dominant usually if family history is studied thoroughly enough, often appears as a recessive   Three sets of twins, two identical, both affected, one fraternal, one twin affected

Laurence Biedl syndrome Recessive   Consanguinity in 7 per cent of 43 cases, an incidence 35 times the normal

Left handedness Usually said to be recessive

Leukemia Recessive usually   One pair of identical twins, both affected, one pair of fraternal twins, both affected

Liver cirrhosis not dependent upon toxic conditions Recessive in all cases   One pair of identical twins, both affected

Monodactyly Dominant in most cases   Two pairs of twins, one affected in each

Niemann-Pick Recessive in all cases   Almost exclusively in Jews   Consanguinity in 14 per cent of the cases, an incidence 70 times the normal

Obesity Dependent upon many factors   Endocrine type usually dominant

Os fragilitas If of the congenital variety, usually recessive   If appearing at a latter age, dominant mostly, although may be recessive   If associated with blue sclerae, almost always dominant   One pair of identical twins both affected, reported

Otosclerosis Due to multiple factors one dominant in the sex chromosome, the other recessive in the autosomes

Oxaluria Dominant in the families reported

Paget's disease Recessive

Pentosuria Recessive

Pernicious anemia Dominant in some instances, recessive in others, and in one family sex linked recessive   Dependent apparently upon other factors besides the inherited ones

Polycythemia Recessive

Polydactyly Dominant in most instances

Polymastia Recessive usually

Porphyrinuria Recessive

Purpura hemorrhagica Dominant in some instances, recessive in others   One instance of consanguinity noted   One pair of like-sexed twins affected

Pyloric stenosis Recessive, probably sex linked   May be due to multiple factors   Much more frequent in the male than female

Spina bifida Recessive in most instances, as far as outward manifestations are concerned   Occult spina bifida may be present in many where its presence is not suspected

Status lymphaticus Recessive where it has been reported as affecting more than one in a family

Steattorhea Recessive and rare

Syndactyly Dominant in most cases

Telangiectasis Dominant in almost all instances

Thrombo angiitis obliterans Sex linked recessive, and mostly found in Jews

Torticollis Recessive

Tumors Mode of inheritance varies apparently in different families, and for different tumors   Some insist on an interpretation of the manner of transmission as simple unit recessive, some as dominant in some cases at least, some that tumors are due to multiple factors   Some find evidence that some of the factors producing tumors are located in the protoplasm of the egg, since there is a higher percentage of tumors in their animals when the mother belongs to the cancerous strain than when the father comes from the cancer family   Due to late age of onset, and predominance of tumors in tissues found only in the female, mode of transmission has been hard to determine

Urobilinuria Dominant in the one family reported with it

Urticaria Irregularly dominant   Dependent upon extraneous factors to evoke the response

Varicose veins Dominant mostly

Zygodactyly Dominant mostly

Twinning Recessive

Diseases of the skin

Adenoides cysticum Few families reported in which this disease had affected more than one member   In one it had occurred through 3 generations in another through two

Adenoma sebaceum Few families reported with more than one affected   These had two or three generations affected

Albinism

   Partial Patches of white skin over the body usually inherited as a dominant condition in families reported   Thus 12 affected through 4 generations, 18 affected through 3, and 15 affected through 4 generations

   Total Always recessive in the cases reported   Consanguineous marriages form 16 per cent of the total cases listed   One instance of an albino produced by a union of a white father with his own mulatto daughter is recorded   The mulatto son of this man and his black wife had leukoderma

Dimples Usually dominant.

Epidermolysis bullosa Dominant in 14 families through as many as 5 generations in some instances   Recessive in 13 families   Forty-six per cent of the matings producing the recessive type were consanguineous   One family with typical sex-linked recessive inheritance

Hair

   Baldness Said to be dominant, passing on from father to son, but recessive in female, requiring double dosage to be effective   Regulated not by sex-chromosomes apparently, but by hormones

   Hypertrichosis Mostly dominant

   Hypotrichosis Mostly dominant, although instances in which it is recessive

   Monilothrix Dominant in most instances

   Nasal brow Dominant

   Premature whitening Dominant in most cases

   White locks or piebaldness Dominant in most cases

Hydroa vacciniforme Sex-linked recessive in most instances

Ichthyosis Dominant in five families through 3 or more generations   Recessive in 8 families, among whom there was 37 5 per cent cousin marriages   Once the marriage was between half brother and sister   In 6 families acted as a true sex-linked recessive   One pair of identical twins, females, reported with condition

Keratoma palmaris Dominant in 30 families, recessive in 4

Keratosis follicularis Sex-linked recessive in some families, dominant in others   Said to be fully developed only when it occurs in the male

Nails

   Various dystrophies Dominant in some families, recessive in a few in which cousin marriages are very frequent, and sex-linked recessive in others, largely depending upon the type of dystrophy in question   Three pairs of twins reported, one pair of females, both affected, one pair of females, only one affected, and one pair male and female, both affected

Naevi

   Small Not obviously inherited

   Large Mostly dominant

Porokeratosis Few families reported with it, but dominant in one family through three generations

Pityriasis Recessive in the few families reported

Psoriasis Said to be parasitic in origin by some, hereditary by others   Dominant through 6 generations in one family, through 4 generations in 2 families   Sex-linked recessive in some

Skin—atrophy of Dominant in the one family reported with it through 4 generations

Teeth
   Congenital ectodermal dysplasia Dominant through 5 and 6 generations in some families, definitely sex linked recessive in others   Associated with lack of hair and absence or diminution of sweat glands
   Faulty enamel Recessive in most instances reported
   Lack of upper incisors Recessive or irregularly dominant in some cases
Xanthoma Dominant in some families through as many as 4 generations, recessive in many others
Xeroderma pigmentosa Recessive in all cases reported   Thirty three per cent cousin marriages in the few families reported with it

Diseases of the eye

Amaurotic idiocy Always inherited as a recessive   Ten per cent of the marriages were consanguineous, an incidence 50 times the normal   Two pairs of like sexed twins with both affected, one pair like sexed twins, one affected, and four pairs, sex not stated, one affected, have been reported
Aniridia Dominant in most families reported, although it sometimes is inherited as a recessive   Is merely the complete expression of coloboma of the iris, and so the two conditions may occur in the same pedigree   One pair of unlike sexed twins, the male affected has been reported
Astigmatism Dominant in the families reported   Some families show the same degree and the same axis of astigmatism inherited from parent to child
Blue sclerae Dominant in the majority of families reported   Occasionally occurs as an isolated case, thus showing its recessive mode also   Occurs frequently with fragile bones, fragility not coming on until several years after birth in most instances   Also frequently associated with otosclerosis
Buphthalmia Recessive in the few families reported with this condition
Cataract
   Congenital Recessive in some families, dominant in others   One pair of like sexed twins both affected have been reported
   Senile Dominant in the vast majority of families reported   Occasionally a parent dies before the cataract develops, but they may have passed it on to their offspring   In a few families it is associated with myotonia atrophica   A history of cataract in the earlier generations, with the myotonia atrophica in the latter generations, is not unusual
Choroiditis Recessive mostly, in those families where infectious causes can be excluded
Coloboma iridis Dominant mostly   Interchangeable in the pedigree with aniridia which is merely a more extensive form of coloboma
Coloboma maculae Dominant in the few families reported with it
Color blindness All forms of it inherited as sex-linked recessive in the families so far reported
Corneal opacities Must first exclude all cases due to infection or injury   Inherited type dominant and recessive in about equal number of families   Where it is recessive, consanguineous marriages were found in 10 per cent of the families
Embryotoxon Dominant in the few families reported
Cryptophthalmus Recessive in few families reported
Day blindness Very rare   Recessive for the most part

Ectopia lentis Dominant in many families, running through some for five generations Recessive in many other families One pair of fraternal twins, both affected has been reported

Epicanthus Dominant in practically all instances

Glaucoma Dominant in most families

Glioma retinae Recessive, practically always Two pairs of identical twins, both affected, have been reported

Heterochromia iridis Rare, sometimes dominant, sometimes recessive

Hypermetropia Dominant

Keratoconus Rare Dominant and recessive in different families

Lagophthalmus Dominant in the one family reported with it

Macular degeneration Recessive for the most part Occurs as the juvenile and adult type of amaurotic idiocy, but is not so fatal One family reported with condition behaving as a dominant

Megalocornea Sex-linked recessive in families reported with it

Microcornea Recessive

Microphthalmus Occurs in some families as a dominant, in others as a recessive and in several as a sex-linked recessive Consanguinity frequent in families in which it occurs as a recessive When it is in its extreme form of anophthalmus, it is almost always recessive, in its milder forms it may be dominant Three pairs of unlike-sexed twins, with the male affected were reported in families where it behaved as a sex-linked recessive

Myopia Said to be recessive in all cases

Night blindness
  With myopia Always sex-linked recessive if associated with myopia, according to some
  Without myopia Dominant in these families in which there is no other eye defect

Nystagmus Said to be sex-linked recessive in those cases in which there is oscillation of the eyes alone Said to be dominant in the families in which a head movement is associated with the eye movement Recessive in a few families

Ophthalmoplegia Dominant in most families In the few in which it was a recessive, there was an incidence of 20 per cent of consanguineous marriages Frequently associated with ptosis

Optic atrophy Sex-linked recessive in 30 families, recessive in 7, dominant in 9 There were 3 families in which part of the pedigree suggested dominance, part sex-linked recessiveness It is possible that both forms of the disease were being transmitted in this family, due to intermarriage of persons, one of whom was carrying the dominant form, the other the sex-linked recessive

Pterygium Dominant in the families reported which showed any inheritance of the condition at all

Ptosis Dominant in most of the families reported with it, although occasional instances of recessive inheritance have been noted

Pupil defects
  Ectopia of the pupil Recessive in some families, dominant in others
  Pin hole pupil Recessive in the few instances reported, parents related Two pairs of unlike-sexed twins reported, one pair both affected, the other only the male affected

Retina
  Angiomatosis Recessive, consanguinity very frequent

Retinitis pigmentosa Eleven types said to exist, of which nine are infrequent, two frequent One of these inherited as a sex linked recessive, the other as a dominant In the literature, I encountered five dominant instances, three sex linked recessive and eighteen recessive, with twelve cousin marriages in the eighteen families, an incidence of 66 6 per cent

Strabismus Dominant in some families, recessive in others

Nervous system

Amyotonia congenita Inherited as a recessive in the 34 families in which more than one child was affected Consanguinity was present in 4 cases or 11 7 per cent, an incidence which was 55 times the normal Two pairs of identical twins both affected, one pair of fraternal twins both affected, and one pair of fraternal twins, one affected, have been reported

Aplasia, extracortical axial Sex linked recessive in most of the families reported with it, although recessive in others Consanguinity in 10 per cent of the cases

Ataxia, cerebellar of Marie Inherited as a dominant in 17 families, as a recessive in 12 One pair of male identical twins, both affected

Friedreich's Inherited as a dominant 21 times, as a recessive in 56 cases Consanguinity in 2 families, or in 2 6 per cent of cases, an incidence thirteen times the normal One pair of identical twins both affected, and one pair of like-sexed twins, one affected reported Latter pair not stated to be identical

Dementia praecox Said to be due to one pair of recessive factors by some workers, and to two sets of recessive factors by others Four pairs of twins with both affected have been reported Two pairs stated to be identical, one pair said to be fraternal, other pair not designated

Epilepsy Where condition is not due to tumor, or to obvious anatomical lesions, is said to be hereditary Is merely a symptom, not a disease in itself, hence varies in its mode of transmission Dominant in some families, recessive in others, its inheritance denied by some workers One pair of identical male twins affected, in which epilepsy was due to spasm of the cerebral blood vessels

Facial spasm Dominant in the families reported as showing this condition

Feeble-mindedness Due to different pathological conditions Supposed to be recessive in extreme cases May be dominant in mild cases

Huntington's chorea Always dominant in the families reported Said by some to be caused by either of two dominant factors, inasmuch as percentage of affected in a family with the disease is much higher than the expected 50

Lateral sclerosis Dominant through five and six generations in some cases Dominant 8 times, recessive 5 In 2 of the 5 recessive instances, there was history of consanguinity, an incidence of 40 per cent, or 200 times the normal

Lenticular degeneration Inherited as a recessive in the 21 families reported as having more than one affected One set of fraternal twins, the male only affected, has been reported

Macular degeneration The juvenile or adult type of amaurotic idiocy In conformity with other diseases, this shows the recessive inheritance in the early fatal cases, of the infantile variety, but may show the dominant type of transmission in the less fatal variety in the adult Inherited as a dominant in five cases, as a recessive in 29 There was a history of consanguinity in parents in 3 5 per cent of the recessive cases, an incidence 18 times the normal

Manic-depressive psychosis Said to be dominant, and more common in males   Identical twins, both affected are reported

Microcephaly Many grades of this defect from the normal to the most microcephalic   In the outspoken cases, inherited as a recessive in the 20 families in which I found it affecting several children in the family   In 4 cases, or 20 per cent, parents were related, incidence 100 times the normal   Three sets of like-sexed twins, and one set of unlike-sexed twins reported, with both twins affected

Migraine Dominant in some families, recessive in others   Term used to designate severe headaches, others than those of the strictly migrainous type, so much confusion exists   Appears to be precipitated by extraneous factors in the susceptible individual, hence its appearance in members of family who have inherited it may be suppressed by lack of extraneous factor in environment

Mongoloid imbecility Inherited as a recessive always   Due to very complex grouping of factors, which make the appropriate combination seldom, thus most cases occur as the only instance in the family   Twins of opposite sex with but one affected, have been reported 17 times   Twins of same sex with but one affected have been reported 20 times   Twins with both affected have occurred six times, and the twins were of the same sex

Multiple sclerosis Inherited as a recessive in almost all cases, although one family has been reported where it ran as a dominant through three generations

Muscular dystrophy Inherited as a dominant in 9 instances, and as a recessive or sex-linked recessive in 51 instances   The parents were related in 6 per cent of the families where recessive inheritance was noted, an incidence 30 times the normal   The males numbered 113 in the recessive group, the females 17, strongly suggesting that sex-linkage occurred in most of the families

Myoclonus Inherited as a recessive in the 17 families found who exhibited it in more than one member

Myotonia atrophica Inherited as a dominant in 9 families, as a recessive in 14

Myotonia congenita Inherited as a dominant in 13 families, as a recessive in 9   One pair of unlike sexed twins, both affected, and one pair of like sexed twins, one affected, reported with this condition   Both of these pairs came from a family in which fraternal twinning was an inherited condition, so that probabilities are that both pairs of these twins were fraternal   Consanguinity in parents was noted in four families where recessive inheritance was present, an incidence of 45 per cent or 90 times the normal

Neuritis, hypertrophic Rather rare to find more than one in a family affected   In one case inherited as a dominant, in 3 as a recessive

Paralysis agitans Inherited as a recessive in most instances, in which more than one member of a family is affected   Many cases occur as the only one in the family, thus obscuring its hereditary nature   One pair of twins, of unlike sex, with the male only affected, has been reported   In one family in which there were frequent cousin marriages, five times cousin marriages gave affected offspring, five times cousin marriages yielded only normal offspring, and 3 non-cousin marriages gave affected offspring, thus suggesting that despite the high incidence of cousin marriages in this family, other factors than inbreeding were responsible for the appearance of the disease

Neurofibromatosis, von Recklinghausen's disease Almost always dominant   May manifest itself only as pigmented areas, or as tumors, or as both   Due to this variation

in appearance of lesion, recessive inheritance may appear as the explanation, when the defect is really dominant in its mode of transmission

Periodic paralysis Inherited as a dominant in most families, although here again, the ability to be precipitated by extraneous factors such as cold, diet, etc , means that the susceptible persons do not always exhibit the disease In some families, periodic headaches take the place of the paralysis, so that the mode of transmission may appear to be erratic

Peroneal atrophy Inherited as a dominant in 25 families, as a recessive in 15, and as a sex linked recessive in one Two pairs of unlike sexed twins, with one pair showing both members affected, the other pair showing the female only affected have been reported

Schilder's encephalitis Noted as occurring as a recessive in five instances

Spastic paraplegia Inherited as a recessive far more frequently than as a dominant One of the commonest forms of nervous disease to be inherited One pair of male twins, both affected reported In the recessive cases, parents were related in 20 per cent of the families, an incidence 100 times the normal

Syringomyelia Inherited as a dominant in five families, as a recessive in nine Occurs for the most part as an isolated example of the disease, obscuring its hereditary nature

Tremor Inherited as a dominant character for the most part

Word blindness Apparently a sex linked recessive in most instances, as the males are far more frequently affected than females, and there is seldom a history of more than one generation affected

This list of diseases and malformations covers the more frequently reported hereditary deficiencies in man The numbers of times that a disease is said to be dominant, or recessive, refer to the instances which I have collected in medical literature, covering a bibliography of 3500 references These are not by any means complete references to *all* cases reported in the literature, but as they are fairly representative of the clinical literature of most of the European and English speaking nations, it is assumed that they are to be accepted as an index of most of the cases that have been reported

There are many rare anomalies which have not been included in this list which are no doubt inherited, but of which I have found no recorded instance where more than one member of the family was affected There are many families reported suffering from some osseous or nervous dystrophy, in which the symptoms are not identical with those of any disease so far mentioned, most frequently the syndrome has not been given a name, and so such records are not here referred to

For discussion of the inheritance of tumors, of some of the commoner types of mental disease see the text

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Note   These are only a small fraction of the 3500 references upon which the conclusions stated in this paper have been based   Owing to the impossibility of including them all, only those which have been specifically referred to in the text have been listed here

THE MUSCULAR ATROPHIES AND ALLIED DISORDERS

CHARLES D ARING AND STANLEY COBB

From the Neurological Unit of the Boston City Hospital and the Department of Neuropathology of the Harvard Medical School, Boston, Massachusetts

Few groups of diseases are so confusing to the physician as the muscular atrophies These conditions have been described under such varying titles and with such wide differences in clinical and pathological findings that only the neurologist can be expected to keep the different syndromes clearly in mind, and too often even he merely memorizes the clinical pictures and attaches to them the name of the original describer without seeing any biological relationships Moreover, the situation is further confused because much of the treatment of these patients is carried on by orthopedic surgeons Thus two specialties, each from its own too narrow point of view, usually divide this small field and all too seldom call upon the internist to obtain his broader view of the relation of the problem to general medicine

A complete review of the literature would be a Herculean task, but we have critically reviewed the principle papers and have listed the interesting original descriptions and the more important modern articles (The writers given as "original" are those with whose names these conditions have become associated Questions of priority we leave to the bibliophile and medical historian) Isolated writings describing these diseases occurred early in the nineteenth century, for example Abercrombie, 1829, Bell, 1830, Rhomberg and Duchene, 1847, and Meryon, 1852 Since then the literature has increased enormously in volume

The etiology of these conditions remains unknown, despite much writing and many speculations Our object in bringing together the main facts in this review is to show that there are no sharp lines between the various syndromes, the very continuity and biological sequence of the phenomena indicate some unknown law behind the whole group It is our hope that with additional facts and a clear

synthesis of data, the etiology may be discovered and a rational therapy instituted.

Muscular atrophy may occur in any condition affecting the ventral horn cell, its axone or the muscle itself   Thus the conditions listed under the heading "secondary" (chart 1) are really true muscular atrophy, but since their cause is known each is listed under another disease entity and treated etiologically   Only the "primary" muscular atrophies remain and make up the group known as "essential" or "idiopathic"   The atrophies of known etiology, however, must not

MUSCULAR ATROPHY

Primary		*Secondary*

Sporadic	*Familial*	

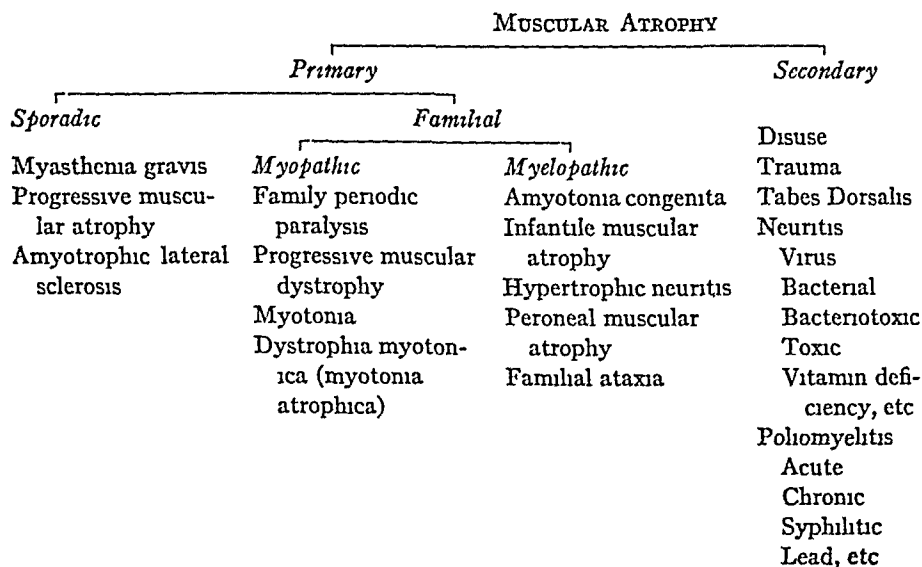|			Disuse
Myasthenia gravis	*Myopathic*	*Myelopathic*	Trauma
Progressive muscular atrophy	Family periodic paralysis	Amyotonia congenita	Tabes Dorsalis
Amyotrophic lateral sclerosis	Progressive muscular dystrophy	Infantile muscular atrophy	Neuritis
	Myotonia	Hypertrophic neuritis	Virus
	Dystrophia myotonica (myotonia atrophica)	Peroneal muscular atrophy	Bacterial
		Familial ataxia	Bacteriotoxic
			Toxic
			Vitamin deficiency, etc
			Poliomyelitis
			Acute
			Chronic
			Syphilitic
			Lead, etc

CHART 1 CLASSIFICATION OF THE MUSCULAR ATROPHIES ACCORDING TO MOST
TEXT-BOOKS OF NEUROLOGY

be overlooked in differential diagnosis, for frequently one sees cases of anterior poliomyelitis (infantile paralysis) or peripheral polyneuritis diagnosed as progressive muscular atrophy, and vice versa   The only safe rule is to study the abnormal physiology, judge what anatomical lesions caused it, and after looking into the history of the case, decide whether any known disease process explains it, or whether the case must be classed in one of the "idiopathic" or "primary" groups
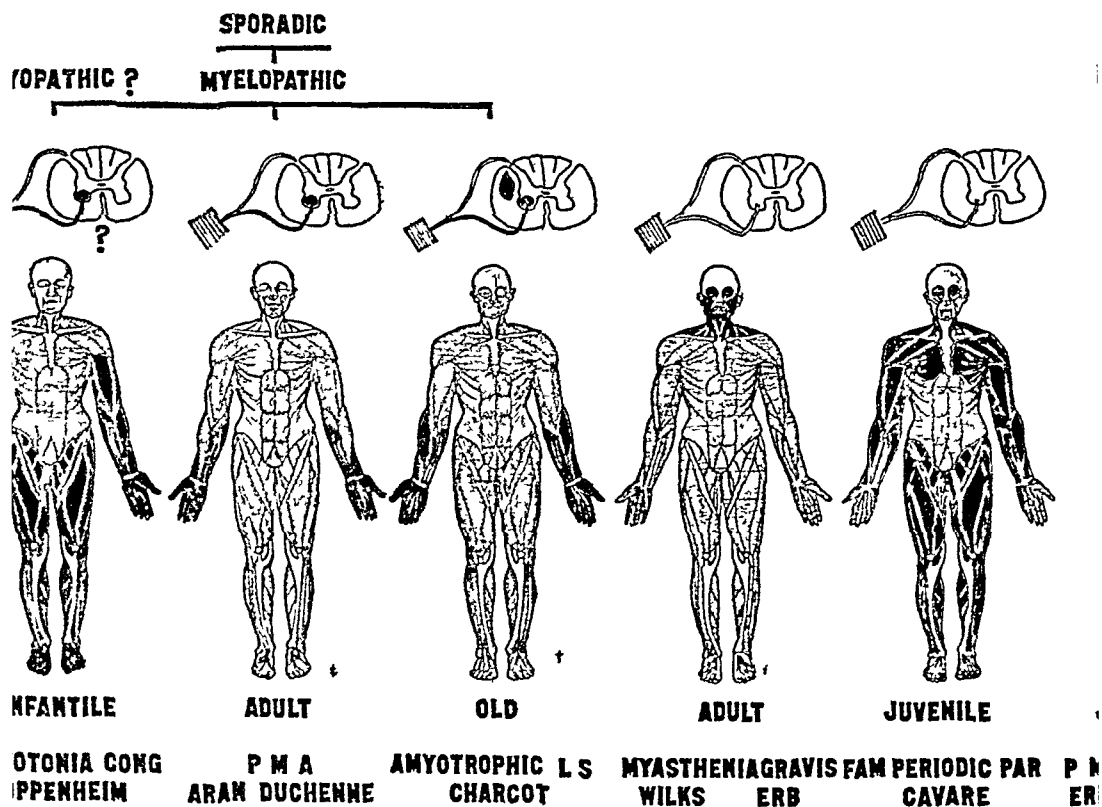
There is only one clear division in the primary muscular atrophies, and that is based on inheritance   Three of the syndromes seem to have no tendency to run in families, these are termed "sporadic"

he nine others all have an hereditary factor, either they are passed
rom parent to child ("vertical inheritance") or they appear in several
iblings of one mating ("horizontal inheritance")   Thus in chart 1
he three forms of primary muscular atrophy at the left constitute a
roup that has no obvious hereditary factor   It must be mentioned,
owever, that *myasthenia gravis*, although a fairly clear-cut disease
ntity, appears to have relationship with diseases of the thymus and
hyroid glands, which have a tendency to run in families   Perhaps
his disease ought not be included because true atrophy of the muscles
s rarely present, but including it at least emphasizes that the diseases
it either end of our chart are connecting links between the obvious
nuscular atrophies and many less strictly myopathic conditions

   Under the two principle divisions, "sporadic" and "familial," sub-
ieadings on a pathological basis can be made   Under each there are
liseases where lesions have been found only in the muscles, and dis-
ases where lesions occur in the spinal cord and peripheral nerve
Thus the terms "myopathic" and "myelopathic" seem to have sig-
uficance and aid us in making some sort of a biological arrangement
if the cases

   Chart 2 is a more ambitious attempt to correlate the known facts
'or reasons given below, myasthenia gravis is put with the familial
nyopathies and amyotonia congenita is moved to the sporadic myo-
>athic group   Each disease entity is represented by a diagram of a
nannikin on which is shown the distribution of the atrophy which is
o varied, and yet so characteristic of each disease   The muscles most
.ffected are made solid black, while those often but not regularly
iffected, are only cross-hatched   This immediately brings out that
he sporadic diseases are more likely to affect the arms and neck, while
he familial diseases may take various patterns, the commonest being
(a) affection of limbs, (b) of hands and feet sparing the trunk, (c) of
.runk and limbs sparing the neck and head, or even (d) of hands and
ieck sparing the trunk   No particular order seems to come out of
.his charting of muscular distribution   Nevertheless, it may be
significant that the myopathic group of familial atrophies seems to
iave rather widespread muscular involvement, whereas the myelo-
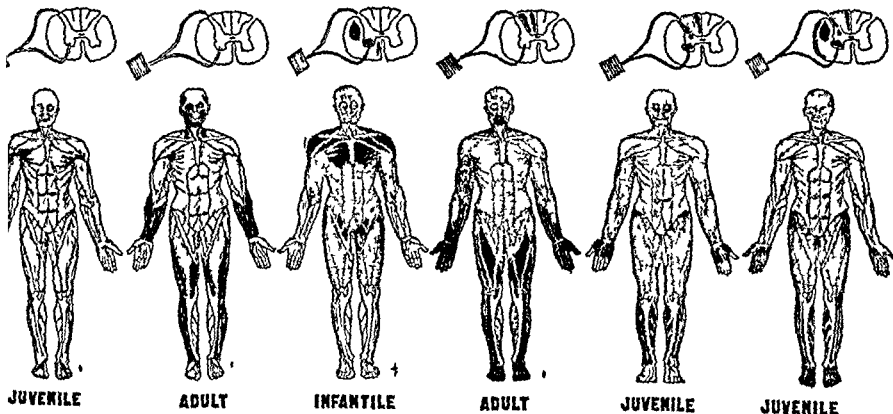>athic group has more specific localization in certain muscles

   The lesions found at autopsy are indicated on the cord-nerve-muscle

SPORADIC

ΊOPATHIC ?   MYELOPATHIC

INFANTILE	ADULT	OLD	ADULT	JUVENILE	
OTONIA CONG	P M A	AMYOTROPHIC L S	MYASTHENIAGRAVIS	FAM PERIODIC PAR	P
PPENHEIM	ARAN DUCHENNE	CHARCOT	WILKS ERB	CAVARE	ER

ATROPHY

FAMILIAL

MYELOPATHIC

| JUVENILE | ADULT | INFANTILE | ADULT | JUVENILE | JUVENILE |
| MYOTONIA THOMSEN | DYSTR MYOTONICA DELEAGE | INFANTILE M A WERDNIGHOFFMANN | HYPER NEURITIS DEJERINE SOTTAS | PERONEAL M A CHARCOT MARIE TOOTH | FAMILIAL ATAXIA FRIEDREICH |

diagrams, each of which is placed above the appropriate mannikin. A brief study of these shows certain important relationships; the pathology of each is given briefly in the text, and the correlations are brought out in the discussion

When we add to the chart the factor of age, making four groups—infantile, juvenile, adult and old—some more interesting generalizations appear Among the familial diseases those which come in infancy have the most widespread muscular destruction, while those that come later in life appear to be more localized to certain muscle groups In the myopathic group the juvenile forms have a more widespread distribution than the one adult form In the familial myelopathic group, the infantile disease is widespread, while the juvenile and adult forms are distinctly restricted Moreover, if the type of inheritance is also recorded, whether it is "vertical" (parent to child) or "horizontal" (several siblings), it is seen at a glance that the diseases with "horizontal" inheritance are those that affect many muscles including those of the trunk Obviously patients so affected are less likely to reach sexual maturity, and even if they do, they are unlikely to propagate

Keeping these relationships in mind, as indicated by the diagram, we proceed to give a brief account of each disease entity

MYASTHENIA GRAVIS (WILKS, 1877 AND ERB, 1878)

The majority of cases occur between the ages of thirty and forty Both sexes are attacked in equal proportion There seems to be no direct familial aspect to this disease, but its relationship to thyroid and thymus pathology brings in the possibility of an hereditary factor

Myasthenia gravis is characterized by abnormal fatigability of the muscles, especially those of the neck, throat, lips, tongue, face and eyes, but all the musculature may be involved, after slight use it may proceed to temporary paralysis Strength then returns on resting In the typical case chewing, speaking or swallowing become difficult and then impossible after relatively brief use of the muscles involved in these movements Sometimes the fatigability begins in the eye muscles with later ptosis and complete external ophthalmoplegia Even repeated stimulation of the eye with light may temporarily abolish the pupillary reflexes The facial muscles also become weak, and sometimes the muscles of the neck are affected allowing the head

to fall loosely backwards or forwards   In the limbs the proximal muscles are chiefly affected   Early in the disease the weakness is transitory, later very little exertion suffices to paralyze the muscle The patients are generally stronger in the morning after a night's rest

Tendon reflexes may grow weaker and disappear with repeated attempts to elicit them   Faradic current applied to affected muscles produces at first brisk contractions, but on repeated stimulation the excitability temporarily disappears (the "myasthenic reaction" of Jolly)   There is no clinical evidence of lesions involving the central nervous system   Actual atrophy of muscle is moderate or absent, no fibrillations are seen, the sphincters are not affected, tendon reflexes are present though fatigable   The spinal fluid is normal

Wolff, Keutmann and Cobb (1928) using the electromyogram, concluded that the muscle exhaustion is due to some fundamental defect peripheral to the ventral horn cell, probably in the muscle cell   Patients with myasthenia gravis usually excrete small amounts of creatine in the urine, although not as much as patients with progressive muscular dystrophy   Cohen and King (1932) in a review of the literature note twenty-four cases of myasthenia gravis associated with exophthalmic goitre   Relatively few cases of myasthenia gravis show evidences of exophthalmic goitre, but the majority of cases of exophthalmic goitre show evidences of myasthenia   They list the following findings that both conditions have in common   (1) hyperplasia of lymphatic tissues, (2) lymphorrhages in the suprarenal cortex, (3) lymphorrhages in muscles, (4) lymphocytosis, (5) lowered carbohydrate tolerance, (6) creatinuria on a diet free from creatine and creatinine

Several investigators (Remen, 1932 and Boothby, 1934) have lately reported benefit from the use of glycine   (Also called glycocoll, amino acetic acid or gelatin sugar) [1]   Glycine is thought to act by building up the phosphocreatine content of muscle, which is believed to play an important part in the contraction of muscle   Boothby (1932), and Beard and Barnes (1931) found that creatine is increased in the muscles of rats following administration of various amino acids, and Lusk (1928) observed that glycine was the only amino acid which caused an appreciable increase in amino acid content of muscle   Harriet Edgeworth, (1930, 1933) afflicted with myasthenia gravis, tells how she

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[1] For method of administration see progressive muscular dystrophy

changed her life from that of a helpless bedfast invalid to a life of moderate activity by using ephedrine, $\frac{3}{4}$ grains daily for three years

Before the advent of these two therapeutic agents most cases gradually weakened until attacks of dyspnea, cyanosis and insomnia occurred, there were remissions, but ultimately the patient became bedridden   The clinical course varied, some few cases proved fatal in months, others lived ten years and longer.   Death usually occurred from exhaustion or pneumonia   Now a large proportion of cases can be benefited by using one or both of these medicaments

Pathology   No significant pathology has been found in the nervous system   The only charactstic eripost mortem finding is the presence of lymphoid cellular deposits in many organs of the body, especially the skeletal muscles   These "lymphorrhages" are found in ill-defined clumps between the muscle fibers and generally in the vicinity of a capillary vessel   There may be a serous exudate   Boothby (1934) suggests that these reactions are due to some type of infecting organism which elects to localize in the muscle   Generally the neighboring muscle fibers are healthy, but occasionally they have undergone degenerative changes   In some cases irregular atrophy of the fibers is found, resembling that seen in progressive muscular atrophy

The thymus gland is abnormal in about one-half of the cases   It may remain large through failure to undergo the normal regressive changes, it may show hypertrophy with degenerative and proliferative changes, or there may be neoplasm

The thyroid is sometimes affected   It has been found to be the site of lymphorrhages, interstitial fibrosis, colloid degeneration of the fibrous stroma and proliferation of the epithelium with the formation of new vesicles   The pituitary in one case presented an adenoma (Buzzard and Greenfield, 1922)   The liver may be the seat of lymphorrhages, especially in the neighborhood of the biliary ducts   (Buzzard, 1905 and Querido, 1929)   The adrenals, kidneys, lungs and pancreas, all have been known to contain lymphorrhages   The bone marrow is normal

PROGRESSIVE MUSCULAR ATROPHY (ARAN, 1850 AND DUCHENNE, 1847)

This disease appears to be a clinical entity, but is with difficulty differentiated from some of the secondary atrophies, notably lead

palsy   It is sporadic and not inherited   The onset is usually in early middle life, rarely before the age of twenty   Men are much more frequently affected than women   The development is insidious   In a majority of cases the muscles of first one and then the other hand are affected   The interosseous spaces deepen, the thenar and hypothenar eminences waste, and a "claw hand" results   The palm of the hand is flattened due to atrophy of the lumbricales, and there are hollows between the tendons of the long flexors of the fingers   Fibrillary twitchings are present both before and during atrophy   Weakness usually calls the patient's attention to his condition   The atrophy advances slowly, sometimes skipping a muscle group to affect another After several years the atrophy may have developed over a greater part of the arm, shoulder, and even the back muscles   Rarely the shoulder and back muscles are the first affected (deltoid, infraspinatus, trapezius, serratus anticus major and others)   The dorsal neck muscles are sometimes involved, even at an early stage   If the disease begins in the shoulder girdle, the arm muscles are next affected and the disease advances peripherally   The lower extremities, if involved, are affected very late, rarely the process may start in the feet

There are no sensory abnormalities   The tendon reflexes of the affected extremities are first diminished and then lost   Electrical examination shows a diminution of excitability corresponding to the disappearance of muscle substance

The disease is chronic and progressive, there may be long remission, but a complete arrest is rare   The duration may be ten to thirty years, life is finally endangered when the respiratory muscles (especially the diaphragm) become involved, or when symptoms of bulbar paralysis make their appearance   Late in the disease signs of involvement of the spinal tracts may appear, thus progressive muscular atrophy may develop into amyotrophic lateral sclerosis

Pathology   The muscles are wasted and look pink or even yellow, they are traversed by fatty streaks   Microscopically the fibers look small and show no striations, but large normal fibers may be found among the atrophied ones   Fibrous tissue is increased   Deposits of granular debris may be seen between the fibres, this may be fatty but no such deposits of fat as are seen in progressive muscular dystrophy are present

changed her life from that of a helpless bedfast invalid to a life of moderate activity by using ephedrine, ¾ grains daily for three years

Before the advent of these two therapeutic agents most cases gradually weakened until attacks of dyspnea, cyanosis and insomnia occurred, there were remissions, but ultimately the patient became bedridden   The clinical course varied, some few cases proved fatal in months, others lived ten years and longer.   Death usually occurred from exhaustion or pneumonia   Now a large proportion of cases can be benefited by using one or both of these medicaments

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In the nervous system one finds degeneration of the ventral horn cells of the spinal cord　The cells are usually shrunken, pyknotic and few in number　There is also secondary degeneration of the ventral roots and peripheral axones　Where bulbar paralysis existed the same degeneration is found in the motor cells of the hind brain　In spite of the lack of clinical signs indicating tract involvement, it is almost invariable to find that changes have also taken place in the pyramidal and other long tracts of the spinal cord　Thus it is evident that progressive muscular atrophy is nothing but an earlier and more slowly developing form of amyotrophic lateral sclerosis in which the pathological process affects especially the spinal and bulbar motor cells

AMYOTROPHIC LATERAL SCLEROSIS (CHARCOT, 1869)

This is a disease of later life, beginning with weakness and atrophy in the hands and arms combined with weakness and stiffness in the legs　Fibrillary twitchings are conspicuous and may precede atrophy in the muscles　Early in the disease, as in progressive muscular atrophy, one arm or leg is usually more affected than the other　The weakness and atrophy progress rapidly, and it is usual to find the patient conspicuously disabled within six months of onset, and bedridden in eighteen months

In the upper extremity the small muscles of the hands are first affected, then those of the forearm, and finally the shoulder girdle　The fibers and muscle fascicles that remain functional are spastic because of lesions in the cortico-spinal tracts, thus the reflexes of the arm may remain exaggerated until loss of ventral horn cells makes the muscular atrophy almost complete　The development of the disease in the lower extremities differs in that atrophy is slight but spasticity is conspicuous, the patient drags himself along with difficulty, the toes clinging to the ground　By this time the disability of the hands has become so advanced that the patient cannot use crutches　Later atrophy appears in the legs, but it never reaches the degree that it does in the upper extremities　The motor cells of the cranial nuclei are usually affected late in the course of the disease, but occasionally bulbar paralysis may occur as the first symptom and comprise the main part of the syndrome　Speech becomes indistinct and nasal, progressing to anarthria, dysphagia occurs, and mastication is often weak

As in the extremities the paresis is accompanied by atrophy of the muscles and exaggeration of tendon reflexes   At first there is found an exaggerated jaw jerk, later even a masseter clonus   Atrophy becomes conspicuous later, the lips are thin, the smile horizontal, the tongue is atrophied and tremulous, and at last lies limp in the floor of the mouth with fibrillary twitchings   The soft palate shows paralysis, and as the masseters atrophy, the lower jaw drops and the mouth hangs open

In the late stage of the disease the spastic limbs may become flaccid, as more and more ventral horn cells are affected   All the motor cranial nerves except those supplying the eye may be affected   The abdominal reflexes often remain present until the disease is well advanced   Babinski and other pathological plantar responses are the rule   Sensation is usually intact   Electrical examination shows quantitative diminution of excitability progressing to complete "R D "   Death occurs most frequently from aspiration pneumonia the expectancy of life after onset is from two to four years

Pathology   The muscle changes are the same as those described under progressive muscular atrophy   In the central nervous system there is degeneration of the ventral horn cells, and the pyramidal tracts show marked loss of myelin and dropping out of axones, all the ventral and lateral tracts are somewhat demyelinated, the dorsal alone standing out dark and normal in the Weigert stain   The nerve cells of the cervical, cranial and lumbo-sacral nuclei are the most affected, they become decreased in number and of those which remain only a few present a normal appearance, most are small, angular and pyknotic Pigment increases, and in some instances, displaces the nucleus to a corner of the cell   There is some compensatory neuroglial proliferation   Similar changes are found in the Betz cells of the precentral convolutions, so the whole of the pyramidal tract shows degeneration Frequently the corpus callosum is atrophied   These central nervous system lesions have the characteristics of a primary process   Perivascular infiltrations are occasionally found, but are so slight as to be considered secondary to the process of degeneration

FAMILY PERIODIC PARALYSIS (CAVARÉ, 1853)

The onset of this condition is usually around puberty, although it has been described in infancy   Males and females are about equally

affected   It is a familial disease, usually occurring in several members of a family   It has been described associated with the occurrence of muscular dystrophies in other members of the family   The literature abounds with description of family periodic paralysis associated with thyroid disturbances   Of Shinosaki's (1926) 24 cases, 14 showed goitre, 6 of which were of the exophthalmic type   He produced attacks by thyroid and parathyroid administrations   Morrison and Levy (1932) report improvement and Dunlap and Kepler (1931) report disappearance of paralytic attacks after relief of hyperthyroidism

These patients, who usually appear otherwise healthy, are afflicted with attacks of flaccid paralysis usually involving the arms and legs, occasionally spreading to all the muscles below the neck   The attacks recur at irregular intervals   The duration of an attack may be a few hours to two or three days   They usually come on at night, the patient awakes to find himself more or less widely paralyzed   If awake the patient notes that his legs are first affected, then his arms, and last the muscles of his trunk and neck   The proximal parts are first affected, the paralysis progressing rapidly distally   The cranial nerves are spared, as a rule, although ptosis is not uncommon   Temporary dilatation of the left ventricle of the heart has been described, the sphincters are rarely affected   The tendon and superficial reflexes are absent

The "cadaveric reaction" in the affected muscles is diagnostic, this is loss of excitability to faradic, galvanic and mechanical stimulation   Between attacks the electrical reactions are normal   Neel (1929) and Zabriskie and Frantz (1932) have repeatedly induced partial attacks by local cooling   The latter authors note that during artificially accelerated recovery (by local heat) the rise of electrical excitability could be followed, while with cooling the steady decrease of excitability could be followed to extinction

The paralysis passes off in a reverse order to that in which it came on   The toes and fingers recover before the proximal muscles   Death has occurred during the attacks, Holtzapple (1905) reporting six deaths in sixteen cases (in one family)   There is a tendency to reduction of attacks in frequency and severity after middle life   Maclachlan (1932) reports the development of permanent muscular weakness, and transition to dystrophy in cases of long standing

Blood chemistry is essentially normal both during the attacks and free intervals   Fluid intake and output is variable and high   Zabriskie and Frantz (1932) note the fluctuation in creatinine output with the patient under standard conditions, and believe this indicates a fundamental disorder of muscular metabolism   They found the oxygen consumption of portions of excised paralyzed muscles about half that of non-paralyzed muscles   Chemical analysis of affected muscles showed low total inorganic phosphate, low creatinine and low organic acid soluble phosphorus

Pathology   Autopsies have been few, and showed nothing definite   Biopsy is either negative or shows a vacuolization of some muscle fibers with a granular substance in these vacuoles   Oppenheim writing in 1900 did not regard these findings as important

PROGRESSIVE MUSCULAR DYSTROPHY (ERB, 1883 AND LANDOUZY, 1884)

According to the distribution and type of the muscular atrophy, many subspecies of this variable disease have been described   We will simplify the situation by mentioning only four principle types   true hypertrophic (Spiller, 1913), the pseudo-hypertrophic (Duchenne, 1860), the facio scapulo-humeral type (Landouzy-Dejerine, 1884), and the distal type (Gowers, 1902)   The first has overdeveloped strong muscles, the "infant Hercules" cases, the next has large weak, rubber-like muscles   The type described by Dejerine is the extreme of local distribution involving the facial, scapular and humeral muscles   In the Gowers' type, on the other hand, atrophy first appears in the hands and feet   There are all grades of intermediate conditions

Onset is usually early in childhood, but some cases have appeared as late as puberty or adolescence   The disease occurs with much greater frequency in the male members of an affected family   The hereditary factor is obvious, some instances having been traced back through six generations   Barnes (1932) found 42 cases in five generations where data were obtainable on 242 individuals, but about 200 members of this family tree had to be left out on account of lack of data

The disease is a combination of atrophy of one group of muscles with pseudo-hypertrophy, this may follow a period of true hypertrophy   The configuration of muscles is altered, some show flattening, others

are enlarged and rounded   The muscles in the stage of *hypertrophia vera* feel like those of an athlete in training, the pseudo-hypertrophic muscles feel firm and rubbery, and despite their apparent hypertrophy they are weak, later they atrophy   Both sides of the body are involved, not always symmetrically   The proximal parts of the extremities are most affected, the distal portions especially the hands and fingers are spared in most cases (except Gowers' type) until late in the disease   The atrophy especially attacks the following muscles· the sternal portion of the pectoralis major, sparing the clavicular portion (Gowers considered this point as important as the hypertrophy of the calf muscles for the diagnosis of progressive muscular dystrophy), trapezius, serratus magnus, latissimus dorsi, biceps, brachialis anticus, quadriceps femoris, and the adductors of the thighs   The pseudo-hypertrophy usually affects the infraspinatus, deltoid, triceps, sartorius, glutei and especially the calf muscles   Where the muscles of the pelvis and thighs and the extensors of the spinal column are involved, the most notable signs are the waddling gait, the lordosis of the lumbar spine (which may also be due to atrophy of abdominal muscles), the protrusion of the abdomen, and the backward slant of the trunk   Almost diagnostic, early in the disease, is the method used by these patients of standing up from a reclining position on the floor   The patient turns on his abdomen, pushes himself up to the hands and knees position (on "all fours"), then one hand is placed on the knee and the body is brought up with a jerk, or the patient "climbs" by working his hands up his legs

"Loose shoulders" result from the atrophy of the muscles which fix the shoulder girdle   During rest the shoulders fall downward and forward, the scapulae stand out from the spinal column and away from the thorax like wings   In a fair number of cases the muscles of the face are involved especially the orbicularis oris and palpebrarum   Globus (1923) has noted changes in the heart muscle similar to but milder than those seen in the skeletal muscle   Iraus (1932) and Boas and Lowenburg (1931) described the abnormal heart rate which is usually rapid with the absence of normal slowing during sleep   They ascribe the tachycardia partly to a diminished venous return flow to the heart due to loss of the pumping action of the striated muscle

Loss of sphincter control is rare in this group   The reflexes are variable, they usually are diminished and are absent only in advanced cases   The affected muscles usually show a lessened excitability to electric current   There are no sensory abnormalities   Numerous congenital anomalies have been reported in association with progressive muscular dystrophy

The course of this disease is extremely protracted, from an insignificant beginning it gradually increases, so it may require years before there is appreciable disturbance of function or extension of the process to other muscles   Along with the insidious development the intact muscles learn to assume the function of the affected ones, and the patient remains a long time active   Cases have been reported extending over forty years   The disease causes death only by the involvement of the respiratory muscles (diaphragm and intercostals) which often results in lung infection   As a rule these patients are short lived, the earlier the onset, the shorter the life

There has been much literature on the etiology and treatment of the dystrophies since the publications of Kure (1930) (1931) and his co-workers   We believe, however, that although his clinical observations are valuable, his physiological explanations are erroneous   The idea that sympathetic fibers directly innervate striated muscle is no longer accepted (Cobb and Wolff, 1932) by most authorities   If Ken Kure's treatment with adrenalin and pilocarpine proves to be effective, it is probably to be explained by the action of these drugs on the fluid environment of the muscle fibers and the resulting humoral changes   The recent work of Loewi (1922), Cannon (1931–1933), Parker (1932), and Wolff and Cattell (1934) show that the autonomic nerves act on smooth muscle and probably on striated muscle by way of chemical changes in the fluid medium

It has long been known that these patients show a creatinuria, excreting ingested creatine in proportion to the severity of the disease Milhorat, Techner and Thomas (1932) giving 15 to 20 grams glycine daily observed an immediate rise in the excretion of creatine (300 to 500 mgm)   After a period of two to eight weeks, there was a decrease in creatinuria, a coincidental rise in creatinine output, and an improvement in the patients' ability to hold ingested creatine   They described the clinical improvement as follows first a temporary "crawling

rumbling sensation" in the muscles, then with further administration of glycine, the hasty fatigability of the muscles disappeared, gradually certain affected muscle groups became stronger and movements which had not been performed for years became possible

The improvement began in from three to nine weeks   In two cases that had shown improvement the glycine was discontinued   The improvement continued three to four weeks, then gradually disappeared, the changes in metabolism corresponding, resuming the treatment again caused improvement after three weeks   Three controls (not suffering from muscular dystrophy) showed none of these changes.

They conclude that glycine has an important function in muscle physiology, and a significant rôle in the pathogenesis and treatment of muscular dystrophy   Reinhold and his co-workers (1934) believe that glycine treatment improves the structure and composition of the muscles (studied by biopsy), but in nine thoroughly treated cases there was no significant clinical improvement

Pathology   Grossly on section the muscles appear yellowish from increased fat in the tissue   Microscopically the connective tissue septa between the muscle fibers appear increased in thickness, and fat is deposited in them   The muscle fibers are of different shapes and sizes   Many are larger than normal and some are small, later in the disease small fibers predominate   In longitudinal section long fibers are seen to break up into two or three segments, each of which may be surrounded by numbers of sarcolemma nuclei, increase in number of the nuclei within the muscle fibers is characteristic   Hyaline degeneration and vacuolation of the hypertrophied muscle fibers are common, in the neighborhood of tendinous attachments the hypertrophied fibers become fibrous   As the disease progresses muscle tissue is replaced by connective tissue and fat until one sees in a microscopic field only a few scattered fibers, some larger than normal, others atrophic.   The walls of the intramuscular blood vessels are thickened and their lumens narrowed by connective tissue proliferation around them   These vascular changes are probably secondary   The nervous system is spared   Chemically Reinhold (1934) has shown that biopsy specimens have an abnormally low creatine content, the fat is increased, water soluble extractives are decreased and total nitrogen is high.

Endocrinology The question as to whether or not the endocrine glands are involved in progressive muscular dystrophy, and if so what glands, is answered in the literature by divergent opinions

Oppenheim (1911) notes a combination of progressive muscular dystrophy and scleroderma, and another with myxedema Prager (1891) reported a case of muscular dystrophy in a patient with hyperthyroidism Boveri (1910) has also reported several cases in combination with exophthalmic goitre, Von Werdt (1908–1909) with colloid goitre Barker (1930) reported a eunuchoid male with dystrophy, Lande (1926) and Schaefer (1932) reported cases associated with adiposogenitalis, Sprunt (1927) referred to the unusual fatty deposits found in the mammary and inguinal regions in this disease Mustafaeff (1929) implicates all the endocrine glands to a certain extent, believing the primary causative factor to be a disturbance of "higher vegetative centers " Jenney, Goodhart and Isaacson (1918) noted dryness and abnormal pigmentation of skin, acromegalic features, brittleness of the hair, hypertrichosis, trophic changes in the nails, unusual distribution of subcutaneous fat, both hypertrophy and under-development of the genitalia, hypoglycemia, delayed glucose utilization, regressive osseous changes, and retardation of bone growth Bone changes of the same type were also observed by Tixier and Roederer (1913), Hutinel (1912), Hahn (1901) and Sterling (1913)

Many authors believe that the pineal gland is abnormal in progressive muscular dystrophy (Goldstein, 1930) (Timme, 1917) Pende (1916) thinks the thymus is involved and Chvostek (1908) the parathyroid In short, there is a mass of clinical data pointing to an endocrinopathic etiology, but much of it is uncritical and must be discarded Even so enough evidence remains to prove that glandular disturbances are often linked with dystrophy in heredity even if they cannot be considered causative

MYOTONIA (THOMSEN, 1876)

Onset is in earliest childhood, but the condition may not be noticed until puberty or later There is little or no progression of symptoms and rarely any improvement Males are more often affected than females This disease is strongly inherited, apparently as a dominant factor

Clinically myotonia is a state of sustained contraction which occurs when the patient attempts voluntary movement after resting At first the contraction cannot be voluntarily relaxed, but after five to thirty seconds the spasm begins to yield, and movements become smoother and easier with every repetition until they can be undertaken without difficulty Therefore a person so affected must "warm up" before undertaking any prolonged task Thomsen, who originally described this condition, had a brother (in his family there were examples in seven generations) who was affected and who was undeservedly punished because in the Army his affliction was not recognized The myotonia is aggravated by emotion, rest, feverish illnesses, forced effort and cold A suddenly attempted energetic movement, such as clenching the first or shaking hands, causes the hand to remain closed for several seconds Warmth has a beneficial effect, as have mental rest, the use of moderate quantities of alcohol, and particularly the frequent repetition of movement Those suffering from myotonia usually have well developed large muscles, but muscular force is diminished All the muscles of the body are usually involved, but the affection may be pronounced in certain parts, and slight in others The ocular muscles may be involved, also the tongue musculature, the muscles of the throat and respiration are rarely affected There is marked exaggeration of mechanical excitability of the muscles Percussion over a muscle gives rise to slow, persistent contraction A deep dimple at the point of impact persists several seconds On electrical examination the nerves react normally Stimulation of muscles with moderate faradic and galvanic current produces persistent contraction ("myotonic reaction") Minimal and momentary stimuli which would not cause normal muscles to contract produce apparently normal contraction in myotonia There are no changes in sensation nor in reflexes

Eulenburg (1887) described a condition called paramyotonia This consists of a rigidity of the muscles of the face and neck, of deglutition and of the extremities coming on in cold weather The rigidity lasts from fifteen minutes to several hours, and is followed by a generalized weakness lasting sometimes for days

Accurately speaking myotonia is a symptom, not a disease When it occurs alone it may be the only manifestation of inherited pathology,

and then one might properly call it a disease entity   Usually, however, the symptom is associated with other glandular, muscular or neural dystrophies   Rosett (1922) points out that these various symptoms may occur together in one individual or be scattered throughout various members of a family   The association seems to be closest to dystrophia myotonica

Pathology   Macroscopically the muscles are slightly paler than normal   They are not fatty   Biopsy shows enlargement of muscle fibers, they are rounder than normal and the transverse striations are poorly marked, the sarcolemma nuclei may be increased in number No changes are found in the nerves and spinal cord

DYSTROPHIA MYOTONICA (DELÉAGE, 1890)

Adie and Greenfield (1923) noted that the recorded cases approached 200, since then many more cases have been recorded   The usual onset occurs between the ages of 20 and 35   Males are more often affected than females (about 5 to 1)   The disease is hereditary, but may not show as myopathy for many generations, the typical myotonia and atrophy being often confined entirely to members of one generation, heredo-familial disease in earlier generations is indicated by cataract, frequent celibacy, many childless marriages, high infant mortality, high birth rate in early generations with low birth rate in later generations, and dying out of branches of the family   Obviously the disease in its full-blown form cannot be inherited, for it destroys the gonads, thus its conspicuous appearance in one generation may mean that this is the last generation of that branch of the family

This is a general dystrophic disorder in which myotonia is often, but not always present   Atrophy is typically found in the facial, neck, sterno-mastoid muscles and the muscles of mastication   This gives the clinical picture of "hatchet face" and drooping head   The forearms, and less often the vasti and peronei are involved, atrophy of the peronei make for a broad-based and steppage gait, superficially resembling the gait of tabes dorsalis   Because of atrophy and myotonia of the oral muscles and of the tongue, the voice is low, monotonous and nasal   In addition to this selective atrophy, myotonia is the most constant symptom   It may be demonstrated in many muscles, but in the great majority of cases it is obvious in the hand grasps alone, as

an inability to open the hand quickly after grasping (see myotonia congenita) Extra-muscular findings are atrophy of the testicles, impotence, baldness, loss of body weight and cataract

There are so many combinations of atrophy and myotonia with other congenital symptoms that it is difficult to describe a typical syndrome In general, weakness of the orbicularis ori and of the sterno-cleidomastoid muscles is almost constantly found, affected early are the muscles of mastication and the temporal muscles, and the first muscle to be affected in the forearms is the supinator longus Atrophy of the dorsiflexors of the feet occur in 50 per cent of the cases From these sites of election atrophy may spread to adjacent muscles, or pick out an individual muscle at a distance, following no known rule Paralysis of the vocal cords has been reported

Cataract is a common finding, Hoffmann (1900) says 10 per cent, Curschmann (1915) notes 30 per cent The onset of the cataract is later in life, the farther one traces back the family tree Baldness, especially in the frontal region, is the most frequent extra-muscular symptom Sometimes there is complete alopecia There may be a generalized scantiness of body hair Atrophy of the testicles is common, sexual function is decreased in both sexes, celibacy and childless marriages appear frequently in the family history A generalized wasting, plus a loss of weight much greater than can be accounted for by muscular atrophy is supposedly due to diminished calcium content of the bones This may account for the bony deformities sometimes seen in this disease The patients are, as a rule, dull, selfish and unsociable; they are often shrewd and difficult to manage, true psychoses have been recorded (Fischer, 1920)

Fibrillary twitchings are rarely present Severe pain in the lower extremities is common, this may be present at the onset The tendon reflexes are usually diminished or absent when muscular atrophy is advanced The myotonic electrical reaction is present as in Thomsen's disease, but as atrophy advances the response to galvanic and faradic current is diminished

The course of myotonia atrophica is very slow, but the patients rarely live to be fifty, they die in exhaustion states, or of intercurrent infection. This poor prognosis may be changed if the new forms of therapy really prove effective

Pathology I Muscular The degree of change in the histological appearance of the muscle appears to vary with the severity of wasting, and to have little or no relationship to the myotonic phenomena Microscopically there is a striking similarity to the changes found in the pseudo-hypertrophic muscular dystrophy, in that the muscle fibers degenerate leaving clumps and chains of sarcolemma nuclei in the connective tissue There is fat deposition Sometimes the striations are preserved in degenerated muscle fibers (It will be observed that this pathology differs from that of the neural muscular atrophies)

II Nervous There are ten cases reported with lesions in the nervous system, but other careful histological examinations have shown nothing Moreover, the neuropathology reported is so varied in location and often so slight in degree, that it may be explained better as the result of a long wasting disease than as the cause of the syndrome

III Glandular Despite the common endocrine symptoms, little attention has been given to the glands of internal secretion at autopsy Naegeli (1917) advanced the theory that myotonia atrophica was the result of a multi-glandular insufficiency Since then six cases have been reported with examinations of these structures Hitzenberger (1920) found reduction of the seminal "lines" and canalicular sclerosis in the testicles There were no changes in the thyroid, parathyroid, thymus, supra-renals and pancreas Bramwell (1922) noted that the thyroid was pale brown, without visible colloid The supra-renals were small and the cortex cloudy and brown Adie and Greenfield (1923) recorded an increase in colloid of the pars intermedia of the hypophysis, and the supra-renals showed a patchy distribution of the lipoids Weil and Keschner (1927) reported the supra-renal cortex pale, yellowish white, the testicles were small and brown, the weight of one testicle was 7 grams (normal 10 5 to 14 grams) There was atrophy of the testicular canals Guillain, Bertrand and Rouquès (1932) noted that their case showed an essentially normal thyroid (some acini were slightly dilated) In one supra-renal there was a tumor of the clear, cortical cells In the hypophysis the pars intermedia showed small colloid cysts The seminal vesicles had disappeared, and in the testicle there were no spermatozoides visible, the interstitial tissue did not show hyperplasia The parathyroid was

essentially normal   Keschner and Davison (1933) found changes in the testes, pituitary and adrenals   On the whole, the clinical and pathological evidence points strongly to endocrinopathy as an important etiological factor

AMYOTONIA CONGENITA (OPPENHEIM, 1900)

This congenital, perhaps familial disease, begins within the first twelve months of life and may be present at birth   Krabbe (1920) noted that 60 cases had found their way into the literature since Oppenheim described the condition in 1901, and of these he was able to find only 4 with heredo-familial history

Clinically this condition is the opposite of myotonia, it is characterized by extreme flaccidity of the muscles, the limbs are most affected, the legs more than the arms, trunk next and the face least of all   The condition is one of weakness with generally small muscles but no true atrophy and no fibrillations   The sphincters are unaffected   The muscles feel soft and lax, the joints are flail-like and can be placed in all sorts of postures   There is no true motor paralysis, although voluntary movements are devoid of vigor   The tendon reflexes are absent   Sensation, speech and mentality are normal   Electrical excitability is diminished (often absent) to both faradism and galvanism, the child can bear strong faradic stimulation with unusual stoicism

A large number of these patients (between 20 to 30 per cent) die in the first year of the disease, if they survive, the disease tends toward slow and progressive amelioration   The tendon reflexes may return, and the patient may learn to walk after several years, but normal muscular power is never attained

Pathology   Grinker (1927) and Greenfield and Stern (1925) have noted the similarity in the pathology of amyotonia congenita and infantile muscular atrophy of Werdnig and Hoffmann   It is possible that the autopsies reported by these authors really represent cases of the latter disease, wrongly diagnosed by the clinician   This is no criticism, for the differential clinical diagnosis between the two is often well nigh impossible   If we accept the spinal cord changes found by these neuropathologists as characteristic of amyotonia congenita, then this condition falls into the myelopathic group, but a few cases have

been reported in which no spinal cord lesions and only slight changes in the muscles were found Krabbe (1920) believes that amyotonia congenita is often confused with the next disease to be described, the infantile muscular atrophy of Werdnig and Hoffmann He considers the former to be a benign disease which consists of congenital hypotonia, hyperflexibility and weakness without muscular atrophy and without myelopathy It is not familial and is perhaps due to retarded development of the musculature These are both rare diseases and more data are needed before the question can be settled

INFANTILE MUSCULAR ATROPHY (WERDNIG, 1890, AND HOFFMANN, 1891)

This is distinctly a familial disease with onset in the first few weeks or months of life No hereditary transmission has been recorded, because these patients do not live long enough Several children of the same parents are often affected

Weakness begins in the trunk and legs with atrophy in the muscles of the back, the shoulder, pelvic girdle and the proximal parts of the limbs It then spreads to the intercostal and abdominal muscles and to the muscles controlling the knee and elbow Actual wasting is not always obvious, because it is as a rule symmetrical and uniform, and may be concealed by fatty tissue Hypertrophy never occurs The condition is slowly progressive and a year or more may elapse before the distal portions of the limbs are affected The diaphragm and muscles supplied by the cranial nerves are spared Late in the disease there may be complete paralysis except for a little movement in the fingers and toes Fibrillary twitchings may be observed

The child lies comfortably in bed, taking nourishment well, although he is completely flaccid Intelligence is normal and sensation is normal The tendon reflexes are absent, or greatly diminished Electrical examination shows little or no excitability to the faradic current This is practically the same picture as has been described in some cases of amyotonia congenita (Krabbe, 1920) Life is usually limited by months, but the patients may live from two to six years after onset Death has been reported because of bulbar involvement, but intercurrent infection is usually the cause

Pathology This resembles that of adult progressive muscular atrophy, but with a proximal rather than distal distribution of paraly-

sis   The anterior horn cells are greatly diminished in number, and are small, some show chromatolysis   The ventral nerve roots are thin, their myelin stains poorly or show evidence of recent degeneration.   The pyramidal tracts are sometimes degenerated   The muscle changes appear to be secondary to the nervous involvement.

HYPERTROPHIC NEURITIS (DEJERINE-SOTTAS, 1893)

The wide variation in symptomatology makes any attempt at describing types of this disease difficult, but two constant clinical features are enlargement of the peripheral nerves with signs of neuritis, and muscular atrophy   It is a rare disease, in a recent review of the literature Wolf, Rubinowitz and Burchell (1932) collected 40 cases (of which they were able to accept 29) and added 3 of their own Thirteen of the 32 had a familial history   The age of onset is usually in the first or second decade, but has occurred as late as fifty.   Males are affected twice as often as females   The course is slowly progressive, rarely there may be remissions

The first symptom is numbness, parasthesia or severe pain in the extremities   Gradual loss of strength in the arms and legs, deformities of the feet, and atrophy are early signs   Later there is usually generalized muscular wasting, the commonly involved groups being the intrinsic muscles of the hands, the flexors of the hands and fingers, the quadriceps femoris, anterior tibials, and the intrinsic muscles of the feet   The polyneuritic picture may vary in type and distribution These nerves are palpably thickened, but sometimes the diagnosis can only be established by biopsy or x-ray   The sensory symptoms may precede, develop with or follow the motor symptoms   Many associated findings have been described, among the most common are pupillary abnormalities, nystagmus, kypho-scoliosis, exophthalmos, diarrhea, ataxia, scanning speech and tremor

The neuritis accounts for a diminution of all forms of sensation Lancinating pains or cramps of the muscles are common   The tendon reflexes are diminished or absent, the superficial reflexes diminished   Babinski reactions have been recorded by Russell and Garland (1930)   About one-third of the cases show fibrillary twitchings The affected muscles give partial or complete reaction of degeneration when tested electrically

This disease is usually slowly progressive, and if intercurrent infection does not occur, life is not materially shortened   Paralysis of the diaphragm has been recorded in one case

Pathology   There is gross hypertrophy of the peripheral nerves, roots and ganglia   This is due to a proliferation of the cells of the sheath of Schwann, producing the concentric laminated structures known as "onion bulbs"   These are diagnostic of hypertrophic neuritis   There occurs a concomitant demyelinization of the axis cylinders, and an associated degeneration of the dorsal columns of the spinal cord   Occasionally the pyramidal tracts are affected, and rarely the optic nerves

PERONEAL MUSCULAR ATROPHY (CHARCOT-MARIE, 1886, AND TOOTH, 1886)

This is a localized muscular atrophy usually beginning in the first decade, although it may be delayed until the second or third   It is strongly hereditary   In Eisenbud and Grossman's (1927) series the transmission was through the males   The number of cases tends to increase with each succeeding generation   Bauer (1924) considers it a dominant character   More males are affected than females

The atrophy begins in those muscles supplied by the peroneal nerves   This causes early foot drop, and there is always a club foot of the *pes equinus,* or the *equino varus* type   Later the calf muscles are involved   The course is slow so it is long before conspicuous atrophy appears   Later the thigh muscles atrophy and after some years the upper extremities may be affected   Occasionally optic atrophy and pupillary abnormalities are described   Electrical testing of the atrophied muscles elicits sluggish response to faradic current   There may be reduced excitability of the muscles of the entire body   Fibrillary contractions are common

Pathology   Changes in the muscles appear to be secondary to the changes in the nerves and spinal cord   The nervous system is affected on both the motor and sensory sides   The most constant findings are degeneration of the ventral horn cells, nerve roots, and some degree of interstitial neuritis in the branches of the peroneal nerves   In more advanced cases one finds degeneration of the dorsal columns of the spinal cord (especially the tract of Goll), atrophy of the dorsal root

occur with or without the special lesions of Friedreich's disease   Optic atrophy may occur with these syndromes, and cases of Leber's hereditary optic atrophy are reported where *pes cavus* and other spinal signs are inherited with the blindness (Merritt, 1930)   Roussy and Levy (1926) describe a syndrome consisting of club foot, ataxia, loss of tendon reflexes and muscular atrophy of the hands, found in seven members of one family   Darré, Mollaret and Landowski (1933) relate this syndrome on the one hand to peroneal atrophy and on the other to Friedreich's ataxia   Weil (1933) mentions the close relationship between these syndromes and the hypertrophic neuritis described by Dejèrine and Sottas   Biemond (1928) reports a family with cases of Friedreich's ataxia, Charcot-Marie-Tooth's peroneal muscular atrophy and deaf-mutism and a second family with cases of peroneal muscular atrophy, Friedreich's ataxia and Déjerine Sottas's hypertrophic neuritis within two generations   The resemblance of the muscular weakness to that of myasthenia gravis has been mentioned   We have seen cases where pes cavus, absent ankle jerks and slight ataxia accompanied epilepsy

Thus it seems that at the right end of our chart, where the more conspicuously neuropathic diseases are placed, the syndromes become more complex and more variable, also the hereditary factor is more remarkable

Pathology   The spinal cord is small, the dorsal roots are degenerated   Sclerosis is most marked in the dorsal columns in which the tract of Goll is more affected than the tract of Burdach   This sclerosis is diminished rostrally   The tract of Lissauer is sometimes involved   The tracts more frequently involved after the above are the lateral pyramidal, and the dorsal spino-cerebellar   In the gray matter the dorsal horns are more frequently involved than the ventral   In a few cases partial destruction of the ventral horn cells is recorded   Clarke's column cells are diminished or degenerated   As a rule the extent of the cord lesions depends on the duration of the disease   The Betz cells of the cortex undergo some atrophy and diminution in number which is secondary to the degeneration in the pyramidal tracts   No constant typical lesion has been found in the cerebellum   Marie established the syndrome of "hereditary cerebellar ataxia" for those cases in which the cerebellum was primarily involved

occur with or without the ...ia myotonica, a disease in which endocrin-
atrophy may occur w...ys a rôle   In myotonia itself, however, the
itary optic atrop...-ndocrinopathic relationship is slight   It rests on the
signs are inherit'nd Kennedy (1924) who believe myotonia to be due to
Levy (1926) des(tivity of the autonomic nervous system   They found
of tendon reflexe)f the myotonic reaction in the affected muscles after
members of one { atropin and thyroid substance, they also noted that
this syndrome or react very little to adrenalin
to Friedreich's a' of myopathies can be made, in which no central nerv-
between these s ns are found, but in all of which there is more or less
by Déjérine ar n endocrinopathic etiology   Unfortunately this evi-
cases of Friedr' rather less than more, but it may point the way to future
atrophy and d s if one emphasizes this aspect, and remembers that endo-
muscular atr(and autonomic nerves are a closely knit system   The old
phic neuritis sympathetic nerves directly innervate skeletal muscles
lar weakness quite thoroughly annihilated, but Cannon's (1931–1933)
have seen (k on substances elaborated by contracting smooth muscle
accompan hin") and Parker's (1932) illuminating studies of the humoral
Thus u sion of nervous impulses, show that the fluid environment of
conspic .scle fiber probably may be changed by sympathetic nervous
more , .rges, and that changes in contractility may result through the
rer ,ence of histamine, acetylcholine or analogous substances (Wolff
...nd Cattell, 1934)

To some it may be necessary to explain why myasthenia gravis is
included among the muscular atrophies at all   Although there are a
few cases in which the weak muscles become atrophied this can hardly
be considered typical   On the other hand, myasthenia gravis appears
to be otherwise related to myopathic syndromes which obviously are
rightly included under the term "muscular atrophy "   For instance,
progressive muscular dystrophy usually shows a creatinuria that is
similar to that found in myasthenia gravis   Moreover, both of these
diseases appear to be benefited by the administration of glycine
dystrophia myotonica resembles myasthenia gravis in that both are
ften associated with similar endocrinopathies, especially hyperthy-
roidism   Coordination of these facts seems to justify the inclusion of
this disease in any study of the muscular atrophies

The familial myelopathic group

The two syndromes known as "amyotonia congenita" or "Oppen-heim's disease" and "infantile progressive muscular atrophy" or "Werdnig-Hoffmann disease" are frequently confused, in fact they may be so similar in their clinical manifestations that differential diagnosis is at first impossible, autopsy reports on the cases with uncertain clinical diagnosis has made confusion more confounded Krabbe (1920) gives evidence which leads us to believe that further careful observations will perhaps put amyotonia congenita into the non-familial group, to be looked upon as a retarded muscular development with no lesions in the nervous system. This attitude towards the diagnosis would transfer to the "infantile progressive muscular atrophy" category all cases that die and show neuropathology

Thus there remains in the familial myelopathic group infantile progressive muscular atrophy, hypertrophic neuritis, peroneal muscular atrophy and familial ataxia   From the pathology it is evident that these four syndromes are neurologically related   All appear to be inherited "system diseases," i e , certain functionally connected groups of neurones degenerate progressively causing increasing symptoms The infantile muscular atrophy shows lesions mostly in the ventral horn cells, but the pyramidal tract is also affected   Hypertrophic neuritis has its conspicuous pathology in the nerve trunks, but there is degeneration of the dorsal tracts and sometimes of the ventral horn cells and pyramidal tract   Peroneal atrophy has definite lesions in ventral horn cells, peripheral nerve and dorsal tracts   Familial ataxia might be looked on as the summation of all these   There are various other rare syndromes, too numerous to mention that result from different combinations of these lesions   For example, congenital optic atrophy may occur with hypertrophic neuritis, with muscular atrophy and with partial Friedreich syndromes   In other words, although the four diseases described are the commonest and the most clear cut entities, so many sub-varieties exist, with so many intermediate and transitional states (e g , the various "formes frustes") that broadly speaking the group is apparently one genus which might be called *familial system diseases of the neuraxis*   Having enunciated this we are free to admit that we have said nothing very enlightening
[1]   the great advances in genetics make it likely that further

accumulation of accurate clinical data will give important leads to the understanding of the great problem of inherited nervous disease, and when these data are complete enough to be of real use to the geneticist, there is hope that methods of prophylaxis may be devised

The sporadic group

The re-arrangements of our chart due to discussion of the data, leaves only three "sporadic" muscular atrophies   Two of these—progressive muscular atrophy and amyotrophic lateral sclerosis—are really one disease   The etiology is unknown but may be an exogenous toxin   The other, amyotonia congenita, is probably due to faulty or delayed embryological development of the peripheral neuromuscular system   Neither of these have much relationship with the familial groups, and when more is known about them they may be transferred to the "secondary" classification   Eventually, therefore, we expect that all "primary" muscular atrophies will be recognized as belonging to the hereditary groups

Type of inheritance

Among the many authors who have written on familial muscular atrophy a few have discussed the type of heredity involved   Most of them have not had data sufficiently complete to justify such discussion Some of them have considered that the inherited factor is recessive or sex-linked recessive   A few (and these are the ones with the widest experience) believe the characters are largely dominant

As Barnes (1932) says "Dominance is a relative term, and all kinds of variations in its degree occur "   This is probably true, but in the two groups of diseases under discussion, it would seem that a better explanation of the irregularities of inheritance was the multiplicity of the factors   For instance, in the myopathic group the factors might tentatively be enumerated as myotrophy, myotonia, lipodystrophy, cataract, alopecia, several glandular dystrophies and factors determining the location of the atrophy, distal, proximal, trunk, facio-scapular, etc   Likewise in the myelopathic group several factors, probably separately inheritable, might be enumerated as possible unit characters   degeneration of ventral horn cells, of pyramidal tracts, of dorsal tracts, of optic nerves, of cerebellar tracts and

a distribution factor   With so many factors it is obvious that one occurring alone may give but slight clinical abnormality and may be overlooked in family histories, only when two or more occur together may the syndrome be conspicuous, and when several concur in one mating the effect may be lethal upon the offspring, causing termination of that line, as in the Werdnig-Hoffmann syndrome and severe Friedreich's disease   The best evidence at present available indicates that these are largely dominant characters, and that the apparent skipping of generations is because slight abnormalities are overlooked

<div align="center">TREATMENT</div>

In recent years some progress seems to have been made in the treatment of the myopathic group   Previously electricity, strychnia and arsenic were exhibited empirically and uselessly   Now the metabolic aspects of myopathy are coming to the fore, and a somewhat more rational therapy is being hopefully essayed   To understand much of this a review of what is known about creatine and creatinine is necessary

Creatine—in the normal   Creatine is said to be a normal constituent of the urine of infants and children in small amounts (10 to 15 mgm per day), increasing during childhood up to ten to fifteen years of age   Light and Warren (1934) found creatine in twenty-four hour specimens of 35 out of 81 normal boys between fourteen and nineteen years of age on an uncontrolled diet   In 8 of these there was over 100 mgm per twenty-four hours   Creatine is also found in the urine of females during menstruation, lactation and after delivery (involution of uterus)   Creatinuria also occurs with acute fevers, acidosis, starvation, excessively high protein diet, low carbohydrate diet (Lusk, 1928), disturbed endocrine functions (hyperthyroidism, hyperadrenalism, infantalism, cretinism, diabetes and other processes associated with deprivation of carbohydrates). achrondroplasia, poliomyelitis, myositis and other diseases involving the muscles

About 98 per cent of the body creatine is stored in the muscles, especially the voluntary groups   Creatine is presumably derived from protein (Peters and Van Slyke, 1931), and serves a useful purpose in the muscles, but the exact method and purpose is not yet clear.

The normal adult excretes daily uniform amounts of *creatinine* in the

urine   (Normal adult male excretes about 1 5 grams in twenty-four hours)   This varies with exercise, metabolic rate, and the diet   The creatinine in the urine is derived from the creatine of muscles and other tissues although this is difficult to demonstrate (Mitchell and Hamilton, 1929) (Peters and Van Slyke, 1931) (Harris and Brand, 1931, 1932 and 1933)   This process seems to be in intimate relation to carbohydrate metabolism (Mendel and Rose, 1911–12, and Brentano, 1932)   Creatinine is derived from and its amount is an index of some special process of normal metabolism taking place largely if not wholly in the muscles   Upon the intensity of this process appears to depend the muscular efficiency of the individual (Mitchell and Hamilton, 1929)   Creatinine is a waste product, its feeding results in almost quantitative excretion   Creatinine excretion is increased in fevers, and lowered in exophthalmic goitre, diabetes mellitus and any condition that results in extreme muscular weakness   It has been claimed that the amount of creatinine excreted bears some relation to the muscular mass, but not to the tension and activity of the muscles (Brand and Harris, 1933)

Creatine—in the muscular atrophies and dystrophies   These patients show a raised creatinuria which increases with an increased protein intake   Unlike normal adults they eliminate a large percentage of small amounts of ingested creatine, this is in proportion to the severity of the disease   With the same level of protein intake the dystrophic patients will usually excrete larger amounts of creatine than comparable patients suffering from other neuromuscular conditions   In far advanced cases, however, they exhibit a lowered creatinuria in proportion to the body weight   The greater the incapacity of the patient, the smaller the daily amount of *creatinine* excretion   The creatinine excretion in most neuromuscular diseases, however, is greater than that found in comparable cases of muscular dystrophy (Harris and Brand, 1933)

The administration of glycine   In 1929, Brand, Harris and Ringer noted that the addition of the simple amino acid, glycine (7 5 grams daily), to the diet of patients suffering from progressive (pseudo-hypertrophic) muscular dystrophy produced an appreciable increase of the creatine excretion in the urine   Larger doses of glycine produced a rise in creatine excretion in some other cases of neuromuscular

atrophy, but usually less than that seen in the cases of dystrophy No appreciable effect was produced on the creatinine excretion by glycine in either type of muscular atrophy   Milhorat, Techner and Thomas (1932) confirmed these findings, and further discovered that in dystrophy, after a period of two to eight weeks (using 15 to 20 grams glycine daily), there occurred a decrease in creatinuria, and a coincidental rise in creatinine output   If the glycine was discontinued the urinary findings gradually reverted (three to four weeks) to those found before the drug was begun   They suggest that the reaction to glycine might be of value in differentiating the dystrophies from the neuromuscular atrophies

The beneficial results (Milhorat, Techner and Thomas, 1932) of the feeding of glycine to patients affected with progressive muscular dystrophy have been discussed under that heading   Others who believe in this treatment are Kostakow and Slauck (1933), Adams (1933), Chanutin, Butt and Royster (1933) and Beard and Tripoli (1933) (1934)   Remen (1932) and Boothby (1932) report beneficial results using glycine in cases of myasthenia gravis   Brand and Harris (1933), giving 7 5 to 25 grams of glycine by mouth daily for a prolonged period (two to nine months) to a series of cases of progressive muscular dystrophy, failed to note any favorable therapeutic effects   They suggest that the variable results obtained by glycine therapy may be due to the difficulty in differentiating the various types of muscle diseases, and that those cases responding to this therapy belong to a special clinical group   Other investigators (Boothby, 1932) (Reinhold, 1934) agree with Brand and Harris as to the poor clinical results obtained in progressive muscular dystrophy

Glycine in some unknown manner acts on the metabolism of resting muscle   In the myopathies the body has lost the ability to utilize creatine   The evidence for this is the creatinuria and decrease in excretion of creatinine, which is probably derived from the creatine of the muscles   This capacity to utilize creatine seems to be regained under glycine therapy   Whether glycine stimulates the production of creatine, or acts in some other manner is not known, this is a difficult biochemical problem

Creatine   Chanutin, Butt and Royster (1933) in a recent communication have reported marked improvement in myasthenia gravis

and in pseudohypertrophic muscular dystrophy with the administration of creatine

Glutamic acid Beard and Tripoli (1933) (1934) have reported benefit in various muscular conditions including progressive muscular dystrophy and "myotrophy from disuse" with glutamic acid—10 grams daily

Ephedrine The use of ephedrine in myasthenia gravis has been touched upon under that heading Edgeworth (1930, 1933) reporting her own case, notes marked improvement under a daily dose of $\frac{3}{4}$ grain of ephedrine sulphate or of ephedrine hydrochloride She has been taking this drug for three years, varying the dose as conditions warrant, without untoward effect from the medication She notes that glycine is without benefit in her case

Cortin Hartman (1933) noted increased efficiency of the muscles in muscular dystrophy under cortin Mendelson (1934) observed marked improvement after 20 doses of 1 cc subcutaneously Bernhardt and Simpson (1932) note that suprarenal extract was ineffective in two cases of myasthenia gravis

Epinephrine and pilocarpine Kure's (1930–1931) hypothesis concerning the sympathetic innervation of striated muscle ("double innervation" and its supposed imbalance in the myopathies) has been touched on elsewhere On this basis he and his co-workers have advocated subcutaneous injections of 0 2 to 0 3 cc of 0 1 per cent solution of epinephrine hydrochloride (adrenalin) and 0 1 to 0 2 cc of a 1 per cent solution of pilocarpine hydrochloride given daily or every second day up to 50 or 60 doses They record good results under this treatment, usually within 50 injections These results are checking of the progress of the disease, and marked improvement, if the condition has not progressed too far Hough (1931) using this treatment and reporting sixteen cases, noted some improvement in every case In four patients the improvement was marked In a later report (1933) he was not so optimistic Voshell (1933) believed that this treatment was justified (16 cases) There are, however, adverse reports and premature enthusiasm is to be deplored

Fetal muscle Parhon and Savini (1914) fed two children suffering from muscular dystrophy with fetal muscle, the idea was to supply essentials which might be lacking for normal muscular development They reported improvement

We have observed one case of progressive muscular dystrophy during a thorough trial with the combination of adrenalin chloride and pilocarpine hydrochloride There was no improvement We have treated five patients over long periods with glycine, of the five thoroughly treated cases, three fall into the familial myelopathic group, and improvement was not expected The remaining two were familial myopathies (dystrophia myotonica and progressive muscular dystrophy) The former three felt (subjectively) stronger, but neither group showed objective improvement

SUMMARY

Summarizing our own experience with myopathy and carefully studying the literature gave us a mass of data which was coordinated under various classifications clinical, pathological and hereditary When reduced to their simplest terms and arranged in the form of a chart, these data seem to throw some light on the biological relationships of the different syndromes Atrophies due to known etiology are classified as "Secondary" and eliminated from the discussion There then remain three groups of "Primary" atrophies (Chart 2) The first is made up of sporadic diseases which probably are not primary atrophies at all, but are perhaps due to some exogenous toxin Secondly, there is a group of hereditary myopathies where the lesions are almost exclusively in the muscles themselves and where there is a significant amount of abnormality of the endocrine glands Lastly, one finds a group, strongly inherited, where the pathology is largely in the spinal cord The syndromes in this group are neurological "system diseases "

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ACUTE SYPHILITIC MENINGITIS

H HOUSTON MERRITT, M D , AND MERRILL MOORE, M D

From the Department of Diseases of the Nervous System, Harvard Medical School, the Neurological Unit, Boston City Hospital and the Boston Psychopathic Hospital

CONTENTS

I INTRODUCTION

Since the syndrome of acute syphilitic meningitis has been known for many years, it is surprising that there are only a few good studies on the subject in medical literature (Gennerich (1922), Nonne (1924), Rothschild (1927), and Moore (1929)) The articles of Rothschild and Moore are the only ones that contain significant data in regard to the ultimate prognosis in these cases

For this reason we undertook to analyze the cases that had been examined and treated by us at the Boston City Hospital during the past six years Since this number was relatively small (24 cases) we have added to them all the cases that have been admitted to the wards of the Massachusetts General Hospital, Peter Bent Brigham Hospital, and the Boston Psychopathic Hospital during the past fifteen years We were surprised at the relatively small number (80) of well-authenticated cases that we could find

In addition, we are presenting a summary of the literature on this subject, with special attention to the symptomatology and prognosis in these cases

Acute syphilitic meningitis, as usually understood and as we use the term here, represents the syndrome which occurs with a flare-up of an infection in the meninges by the treponema pallidum   This inflammation of the meninges manifests itself clinically by the occurrence of the symptoms of headache, nausea, vomiting, and stiffness of the neck with or without signs or symptoms of involvement of the meninges at the base of the brain (cranial nerve palsies) or the meninges over the vertex (mental signs, convulsions, etc)   The blood Wassermann reaction may be positive or negative   The cerebrospinal fluid is increased in amount, and the pressure is elevated   There is a pleocytosis of varying degree, and a positive Wassermann in the cerebrospinal fluid

Although acute syphilitic meningitis had been known as a complication of both early and late syphilis for many years before the introduction of salvarsan therapy, there was an apparent great increase in the number of these cases immediately afterwards   It was thought that this increase was the result of the salvarsan therapy and it was postulated that the spirochetes had been driven into the nervous system by the arsenical treatment thus precipitating a flare-up in the meninges The term "neurorecurrence" was applied to these cases by Ehrlich, emphasizing the fact that the central nervous system was involved at a stage of the infection when it was usually spared

For many years there was a great deal of discussion as to the rôle played by arsenic in producing or precipitating the meningitis   With the advance of our knowledge regarding the involvement of the meninges by syphilis, it became evident that some degree of meningitis was present in the majority (60 to 80 per cent) of the cases of syphilis during the secondary stage as a result of the dissemination of the spirochetes at this time, and that symptoms of this involvement in the form of an acute syphilitic meningitis occurred in cases that had received no treatment, or only bismuth or mercury therapy, as well as in cases which had been given arsenical treatment

Stokes (1928) presents very concisely the best opinion in regard to this controversy. "Neurorecurrence is not to be confused with a

therapeutic shock or Herxheimer reaction, nor is it to be regarded as evidence that 'arsenic' has 'predisposed' the nervous system to spirochetal invasion   It is merely a relapse of an imperfectly extinguished infection in a structure peculiarly inaccessible and difficult of sterilization and in a patient whose resistance has been prevented from developing by improper treatment   The remedy for neurorecurrence is more intensive treatment for syphilis   "

Clinical attention was first drawn to acute syphilitic meningitis by the studies of Lefeuvre (1866) but the syndrome was not clearly crystallized until the studies of Benario (1911), Ellis (1912), Gennerich (1922), Nonne (1921), Zimmerman (1922), Pette (1924), Rothschild (1927), and Moore (1929)   In the past ten years there have appeared many articles on this subject   Most of these, however, have been restricted to the clinical description of a few cases and to the pathological examination of single cases   The studies of Rothschild and of Moore are the only ones that contain data on a large series of cases which have been followed long enough to give any information as to the ultimate prognosis in these cases   These two series will be used in comparing the results obtained in our own series

II ANALYSIS OF CLINICAL MATERIAL

In selecting our material, cases were chosen to conform with the criteria above-described   All cases were excluded in which the history was inadequate or the diagnosis was not confirmed by examination of the cerebrospinal fluid   We were at once impressed by the fact that acute syphilitic meningitis is a relatively rare occurrence   We were able to find only 80 well-authenticated cases in the records of three general hospitals in the past fifteen years   This is in agreement with the statement of Stokes that neurorecurrences are comparative rarities even in special practice, and with Moore's statement that neurorecurrences occurred in 0 2 per cent of 2,675 cases of early syphilis   It is in disagreement, however, with the statement of Finger (1911), who found neurorecurrences in 9 0 per cent of 500 cases of early syphilis

We have analyzed our 80 cases with the view of obtaining information in regard to the following points

(1) The clinical character of the syndrome of acute syphilitic meningitis

(2) The effect of previous therapy on the onset of the meningitis

(3) The immediate results of treatment in all cases, and the ultimate prognosis in the cases that have been followed over two years

(4) A complete analysis of the cerebrospinal fluid findings in these 80 cases

(5) In addition we are reporting the pathological findings in 1 case where the patient died following an operation for decompression of the brain

In analyzing our 80 cases, we found that they fell into three groups, according to signs indicating the site of the most marked involvement of the meninges, as follows

Group I Acute syphilitic hydrocephalus (26 cases) In this group the symptoms were limited to headache, nausea, and vomiting The examination of the nervous system showed only stiffness of the neck, Kernig's sign, and choked discs The occurrence of headache, nausea, and vomiting, with choked discs is characteristic of an acute hydrocephalus, and its presence in these cases, in connection with meningeal signs and serological evidence of syphilis, justifies the designation of this group as acute syphilitic hydrocephalus The development of the acute hydrocephalus in these cases is due to a disturbance in the cerebrospinal fluid circulation, and it is probable that in these cases the chief involvement of the meninges is in the posterior fossa obstructing the flow of the fluid from the basal cisterns

Group II Acute syphilitic meningitis of the vertex (20 cases). In these cases convulsions, focal phenomena, or mental symptoms occurred, in addition to the general signs and symptoms of meningeal involvement The symptoms of convulsions, focal phenomena (such as hemiplegia and aphasia), and mental signs are those commonly seen in disorders of the meninges over the convexity or vertex of the brain, and we have, accordingly, designated these cases as acute syphilitic meningitis of the vertex

Group III· Acute syphilitic meningitis, basilar type (34 cases) The third group is composed of cases which showed cranial nerve palsies Paralysis of the cranial nerves is explained only on the basis of involvement of the meninges around these nerves at the base of the brain These cases are, therefore, called the basilar group This constitutes a much larger group than either of the other two, and includes 34 of our 80 cases

These groups are not mutually exclusive, but remarkably few cases show evidence of a mixture of types   In the first group there was no evidence of involvement of the meninges at the base with cranial nerve palsies nor were there any convulsions, focal or mental signs indicating involvement of the meninges of the vertex   In the second group, however, there were 2 cases with cranial nerve palsies, indicating involvement of the meninges at the base, and in the second and third groups there was a considerable number with choked discs, indicating an interference with the cerebrospinal fluid circulation   The infrequent occurrence of this mixed type is also indicated in the literature by the rarity of such cases   Moore does not record any examples in his 81 cases, nor does Gennerich in 25 cases

Group I   Acute syphilitic hydrocephalus

This group consists of 26 cases with the presenting symptoms of headache, nausea, and vomiting only   Neurological examination showed stiffness of the neck, Kernig's sign, and choked discs, without evidence of focal lesions or cranial nerve palsies   These signs and symptoms are interpreted as indicating a localization of the meningeal involvement in the posterior fossa

A summary of the clinical history and serological findings in these 36 cases is given in table 1

Sex and age distribution   There were almost twice as many males as females in this group   seventeen were males, and nine were females —a matter which will be discussed later   The ages varied from 12 to 56 years with a mean of 29 years   Case 19, a 12-year old congenital tabetic, was the youngest case   Twenty-two (88 per cent) of the remaining 25 cases were between the ages of 19 and 39 years   This would indicate that while syphilitic meningitis may occur at any age, it is most common in young adults   This is to be expected since the meningitis is ordinarily an early complication of the syphilitic infection, which is usually acquired during the sexually active years

Time of onset of the meningitis   In 18 of the 26 cases, the time of the primary infection was known   One case occurred in a congenital tabetic   In 7 cases (27 per cent) the meningitis was the first evidence of the syphilitic infection   These 7 patients (5 male, 2 female) had no knowledge of a primary sore or secondary rash, and had not re-

ceived any anti-luetic therapy. The frequency of the occurrence of neurosyphilis as the first known manifestation of a syphilitic infection has been emphasized by Gennerich. In the 18 cases in which the

Acut.

CASE NUMBERS	HISTORY OF CASES					SYMPTOMS		NEUROLOGI	
	Initials	Age	Sex	Time after infection	Previous treatment	Duration of symptoms	Headache, nausea and vomiting	Stiff neck and Kernigs' sign	Choked disk
1	V Y	35	M	2 mos	None	2 wks	+	+	0
2	R C	28	M	4 mos	Sub standard	2 wks	+	+	+
3	I O	29	F	4 mos	Sub-standard	5 wks	+	+	+
4	L D	20	M	4 mos	Standard	3 wks	+	+	0
5	W P̆	26	M	4 mos	Sub-standard	1 mo	+	+	—
6	F L	33	M	5 mos	Sub-standard	1 wk	+	+	+
7	J H	56	M	5 mos	Sub standard	1 wk	+	0	+
8	H M	33	M	6 mos	Sub-standard	2 wks	+	+	0
9	J T	26	M	7 mos	Sub-standard	3 wks	+	+	+
10	R C	24	F	7 mos	Sub-standard	8 wks	+	+	+
11	F C	36	M	7 mos	Sub-standard	3 wks	+	+	+
12	J B	30	M	8 mos	Sub-standard	2 wks	+	+	0
13	T M	41	F	9 mos	Sub-standard	3 mos	+	+	+
14	M D	27	F	11 mos	Sub-standard	3 wks	+	+	+
15	M P	23	F	1 yr	Sub standard	2 wks	+	+	+
16	M P	24	F	1 yr	Sub-standard	3 wks	+	+	+
17	L R	19	F	1½ yrs	Sub standard	2 wks	+	+	+
18	J P	40	M	6 yrs	Sub-standard	1 wk	+	0	0
19	H D	12	M	Congenital	Sub-standard	1 wk	+	+	+
20	C M	20	F	?	None	2 wks	+	+	+
21	J S	21	M	?	None	2 wks	+	0	—
22	C F	23	F	?	None	8 wks	+	+	+
23	W H	29	M	?	None	3 wks	+	+	0
24	P M	35	M	?	None	4 wks	+	+	+
25	L L	36	M	?	None	4 wks	+	+	+
26	A S	39	M	?	None	2 wks	+	+	0
High .		56				12 wks			
Low		12				1 wk			
Mean .		29				3 wks			

* Subsequently weakly positive.

time of infection was known, 16 (89 per cent) occurred during the first year of the infection. The remaining 2 cases occurred within six years after the appearance of the chancre. Acute syphilitic hydrocephalus

is predominantly a complication of early syphilis, but that it may oc-
cur in the late stages is shown by case 18, in which it occurred six years
after the infection   In cases 20 to 26 inclusive, it is impossible to tell

Per cent polymorpho-nuclear leucocytes	Globulin reaction	Total protein (mgm per 100 cc.)	Colloidal gold curve	Sugar (mgm per 100 cc.)	Chlorides (mgm. per 100 cc.)	Cerebrospinal fluid Wassermann reaction	Period followed	Treatment	Clinical results	Final serological status
70	10	+		51	717	Positive	2 yrs	Standard	Recovered	Unknown
75		+	62 0122100000			Positive	2 yrs	Standard	Recovered	Normal
30		+				Negative	2 yrs	Sub standard	Improved	Improved
25	5	++	282 5554323000			Positive	8 mos	Sub-standard	Improved	Improved
00	20	++				Positive	9 yrs	Standard	Recovered	Normal
30	5	−	224 0001122100	76	710	Positive	2 yrs	Standard	Recovered	Normal
35		++				Positive	5 yrs	Standard	Recovered	Normal
97	18	+				Positive	1 yr	Sub-standard	Recovered	Unknown
34		++	82 0112210000			Positive	8 mos	Sub-standard	Improved	Improved
42	0	0	23 0000000000	62		Negative*	5 yrs	Standard	Recovered	Normal
50	5	++	88 0012231000	39	702	Positive	5 mos	Sub-standard	Improved	Normal
40	30	++				Positive	2 yrs	Sub-standard	Improved	Unknown
17	0	+	53 0001121100	65	739	Positive	2 yrs	Standard	Recovered	Normal
82	20	++	114 5555555440	26	649	Positive	2 yrs	Sub-standard	Recovered	Improved
26	0	0	31 0001000000	59	695	Negative	2 yrs	Standard	Recovered	Normal
85	15	++	59 0012223210	37	649	Positive	1 yr	Sub-standard	Recovered	Normal
91	10	++				Positive	1 mo	Sub-standard	Improved	Unknown
58	15	+	43 0123332111	50		Positive	2 yrs	Sub-standard	Tabes	Improved
30	56	++	82 1112211000			Positive	5 yrs	Standard	Improved	Unchanged
515	10	+	168 0000123322	23	702	Positive	3 mos	Sub standard	Improved	Improved
528	20	++	75 5555543210	53	731	Positive	1 mo	Sub-standard	Improved	Improved
600	2	++	5555431000			Positive	1 mo	Sub-standard	Improved	Improved
180	5	++	98 0001121000	67	728	Positive	1 mo	Sub-standard	Improved	Improved
14	0	+	125 2235555710			Positive	5 yrs	Sub-standard	Improved	Unknown
520	14	−				Positive	1 mo	Sub-standard	Improved	Unknown
920	10	++	189 0011222210	32	636	Positive	2 yrs.	Sub-standard	Recovered	Unknown
600	56		282		76	728				
14	0		23		23	636				
495	12		105		49	695				

at what age the meningitis developed, but it is probable that the ma-
jority were also early cases because of the excessive predominance of
the early cases in the group in which the time of infection was known

The earliest development of symptoms was two months after the appearance of the chancre (case 1)   It is not rare for the meningitis to occur so soon after the infection   Read (1915) reports a case that developed meningitis two weeks after the appearance of the chancre, but it is more usual for the symptoms to become manifest three to seven months after the primary infection

In 12 of the cases (46 per cent) a history of a secondary rash was given   The data in the records was usually not detailed enough to determine the nature or severity of the muco-cutaneous secondary manifestations   The frequency of a history of secondary rash in these cases of meningeal syphilis is in contrast with the infrequency of a history of such lesions in parenchymatous neurosyphilis

Previous treatments   In 8 cases (30 per cent) there was no history of any previous anti-luetic therapy, and only one patient (case 4) was receiving treatment when the meningeal symptoms developed   In this patient the meningitis developed while he was receiving mercurial injections   His treatment before admission to the hospital consisted of eight intravenous injections of arsphenamin, and twelve intramuscular injections of mercury   In all of the remaining 17 cases, the meningitis developed after a lapse in treatment varying from one to seven months, with the exception of case 18, which developed meningitis two years after mercurial injections   Only 2 cases (case 13 and 14) had received intramuscular injections of bismuth prior to the onset of the meningitis, the meningitis developing in case 14 five months after the patient had lapsed from treatment   She had received twenty intravenous injections of neo-salvarsan and seven injections of bismuth during the first six months after the appearance of the chancre   In case 13, the meningitis developed nine months after the primary infection, and six weeks after a lapse from treatment   This patient had a primary infection in April, 1931   She received twelve intravenous injections of arsphenamin (0 35 gram each) from April to May, 1931, and ten intramuscular injections of bismuth from June to October, 1931, and seven more injections of salvarsan in November and December, 1931   She lapsed from treatment and was admitted to the hospital on February 22, 1932 with acute syphilitic meningitis

To summarize· meningitis developed in 8 cases that had no pre-

vious treatment, in 16 cases that had received arsenical and mercurial treatments, and in 2 cases that had received arsenical and bismuth treatments   The meningitis developed in 1 case while under active mercurial therapy   It did not, however, develop in any patient receiving active arsenical or bismuth therapy   The occurrence of the meningitis in the 8 cases that had received no previous treatment, shows conclusively that the precipitation of the meningitis is not related to arsenical therapy

Symptoms   Symptoms of an acute hydrocephalus—headache, nausea, and vomiting—were present in all 26 cases   The duration of symptoms before admission to the hospital varied between one and twelve weeks   In the majority of the cases, 22 out of 26 (85 per cent), the symptoms had been present less than one month before admission   In some of the cases there was a variation in the intensity of the symptoms before entry to the hospital, but in most instances there was a steady progression of the disease   In the cases with history of a primary lesion and of previous treatment, the diagnosis was made in the out-patient department or admitting office of the hospital, but in the 7 cases without a history of syphilis, the diagnosis was made only after lumbar puncture   This fact is of considerable significance, and shows the importance of considering syphilitic meningitis in such cases   The value of the lumbar puncture in obscure disturbances of the nervous system is dramatically demonstrated since 5 of these 7 cases had a negative blood Wassermann reaction   The cerebrospinal fluid of all 5 cases showed a strongly positive Wassermann reaction, and 4 of the cases had more than 500 cells per cubic millimeter of the fluid   If lumbar punctures had not been performed in these patients (in spite of "choked discs") they would possibly have been subjected to exploratory craniotomy or ventricular air injections

Neurologic signs   Evidence of meningeal irritation, i e , stiffness of the neck and Kernig's sign, was present in 23 of the 26 cases (85 per cent)

The pupillary reactions to light and on convergence were *normal in* all cases with the exception of cases 18 and 19, which had Argyll Robertson pupils   Of these, case 18 had a syphilitic infection of six years duration, and case 19 had congenital tabes   In several of the remaining cases, the pupils were stated to be slightly irregular   The

finding of normal pupillary reactions in these cases is in accord with the concept that the abnormalities in the pupillary reactions in neuro-syphilis have a very slow evolution and these observations are of considerable importance in regard to the controversy as to whether Argyll Robertson pupils are due to a lesion of the nerve and tract-fibers, or to a more centrally placed lesion

There was no evidence of involvement of the cranial nerves in this group, with the exception of the fact that choked discs were present The choking of the optic nerve-head was not interpreted as evidence of primary involvement of the nerve proper, but was considered to be due to the increased intracranial pressure   The degree of visual impairment in these cases was no more than could be accounted for by the swelling of the nerve   Choked disc was present in 17 of the 23 cases (73 per cent) in which the examination of the fundi was recorded The severity of the choking varied from an obliteration of the disc margin to three or four diopters of swelling

The reflexes did not present any evidence of focal disease in the form of inequality of the deep reflexes on the two sides or of abnormal plantar response   Indeed, with the exception of the case of congenital tabes in which the reflexes, of course, were absent, there was no evidence of reflex change, although in 8 cases the deep reflexes were rather lively and might have indicated an irritation of the pyramidal tract

Serology.   The serological findings in these patients on admission to the hospital are presented in table 1, and they will be discussed more fully in connection with the findings in the other groups

It is of considerable importance to emphasize here the unreliability of the blood Wassermann test in these cases   In the 23 cases in which the blood Wassermann was recorded, the test was positive in 16 (70 per cent) and negative in 7 (30 per cent)

The cerebrospinal fluid Wassermann test was positive in 23 cases (89 per cent), and negative in 3 cases (11 per cent)   The finding of a negative cerebrospinal fluid Wassermann reaction is not new or rare in these cases, and it should be emphasized here that other evidences of abnormalities in the cerebrospinal fluid were found, such as a pleocytosis, positive globulin test, and abnormal colloidal gold test They are sufficiently unusual, however, to justify presentation of a brief summary of these cases

Case 3 I O , a 29-year old white female, had a secondary rash four months prior to entry to the hospital on May 20, 1922   She was treated by five injections of arsphenamin, with disappearance of the rash   Two weeks before entry there was an acute onset of headaches, nausea, vomiting, and tinnitus   These symptoms persisted and increased in severity until entry to the hospital   Neurological examination showed only a slight stiffness of the neck and choked discs   The blood Wassermann reaction was positive   The cerebrospinal fluid contained 630 cells, chiefly lymphocytes, a markedly positive globulin reaction, and a negative Wassermann

The case was treated in the hospital by the intraspinous method of Swift-Ellis, with rapid improvement   She was followed for two years, receiving irregular treatment in the out-patient department   At the end of this time the blood Wassermann reaction was still positive   The cerebrospinal fluid showed nine cells, and a positive globulin reaction   The colloidal gold test and cerebrospinal fluid Wassermann were negative   The patient was then lost to the clinic

Case 10 R C , a 24-year old female was admitted to the hospital March 17, 1928   Seven months previously a secondary rash appeared when she was two months pregnant   She was then given six injections of sulph arsphenamin, and six injections of mercury   In the last two months of pregnancy she complained of fever, headaches, and stiff neck   She was admitted to the hospital seven days after the delivery of a normal boy   She was stuporous and showed stiffness of the neck, and choked disc   The blood Wassermann was negative   The spinal fluid was under pressure of 240 mm of spinal fluid, and contained 42 cells per cubic millimeter   The globulin tests were negative, total protein content was 23 mgm per 100 cc , and the cerebrospinal fluid Wassermann was negative

She was treated intraspinously after the method of Swift-Ellis   The cerebrospinal fluid which was obtained ten days after the first puncture showed a weakly positive Wassermann reaction   She was discharged from the hospital symptom-free after three weeks of treatment, and was followed for five years in the out-patient department with active treatment for the first year and a half   At the end of this time the blood Wassermann was negative and the cerebrospinal fluid was entirely normal

Case 15 M P , a 23-year old female was admitted to the hospital on April 6, 1932   She gave a history of a secondary rash one year before entry, at which time her blood Wassermann reaction was positive   On account of very small veins, she was treated by her local physician with intra-

muscular injections of mercury   Two weeks before entry to the hospital she began to suffer with headaches, nausea, and vomiting   On admission she was semi-stuporous, with stiffness of the neck and choked disc   The blood Wassermann was positive   The cerebrospinal fluid, was under a pressure of 310 mm of cerebrospinal fluid, and contained 26 lymphocytes per cubic millimeter   The globulin test was negative, and the total protein content was 31 mgm per 100 cc , sugar content 59 mgm , and chlorides 695 mgm per 100 cc   The colloidal gold and Wassermann reactions were negative

The patient was treated in the hospital by intravenous injections of neo-arsphenamin, and was discharged symptom-free   She was treated in the out-patient department for two years and at the end of this time the blood Wassermann was negative and the cerebrospinal fluid was entirely normal

Results of treatment   Since the patients in this study were treated at various hospitals, and since the study covers a fairly long period of time, there was no uniformity in the treatment received   Fourteen of the patients received intravenous injections of an arsenical drug and intraspinous therapy (Swift-Ellis method) while in the hospital, and 12 were treated only by intravenous injections of salvarsan or neosalvarsan   In addition, the rest in bed and repeated lumbar punctures were possibly important factors in the therapy of the patients All of the patients received an arsenical drug intravenously, either alone or in connection with Swift-Ellis intraspinous treatment, and in every case there was a rapid disappearance of the symptoms which caused entry to the hospital, the average stay in the hospital being eighteen days

After leaving the hospital, 14 of the patients were followed for periods varying from two to nine years   Eight of these patients attended the clinic regularly and received what is considered to be standard or good treatment, i e , continuous treatment for at least eighteen months to two years with alternate courses of an arsenical drug, and a heavy metal (mercury or bismuth)   The cerebrospinal fluid was examined at the end of the period of observation in all 8 cases   In 7, the fluid was entirely normal and the patients were clinically recovered   The remaining case (no 19, a congenital tabetic) showed no significant change in the clinical syndrome or serological findings after five years of treatment

Six of the 14 patients who were followed more than two years attended the clinic irregularly and did not receive standard treatment Five cases were clinically recovered In 3 of these cases (nos 12, 24, and 26) no final examination of the cerebrospinal fluid was obtained, and in 2 cases (nos 3 and 14) the cerebrospinal fluid showed persistent abnormalities One case (no 18) was followed for twenty-six months, at the end of which time he showed the typical syndrome of tabes dorsalis A brief summary of his case is presented below

Case 18 J P , a white, Italian-born barber, aged 40, was admitted to the hospital July 2, 1931, complaining of weakness, severe headaches, and vertigo He gave a history of a primary sore and a secondary rash six years previously He was treated with intravenous injections by his local physician, the exact number not known He had a negative blood Wassermann two years before admission and had received no treatment since then

On admission, the examination was negative except for irregular pupils, which did not react to light, and hyperactive deep reflexes The blood Wassermann reaction was positive The cerebrospinal fluid pressure was 220 mm The fluid contained 58 cells per cubic millimeter, total protein of 43 mgm and sugar 50 mgm per 100 cc The colloidal gold reaction was 0123332111, and the spinal fluid Wassermann reaction was positive

The patient was treated in the hospital by intravenous injections of neosalvarsan with rapid subsidence of headache and dizziness He was followed in the out-patient department and during the next twenty-six months he received nine intravenous injections of neosalvarsan, thirty-five injections of tryparsamide, and fifteen intramuscular injections of bismuth He began to complain of shooting pains in his legs, and examination on November 28, 1933, showed typical Argyll Robertson pupils, absent ankle jerks, diminished vibratory sense in the legs, and a slightly positive Romberg sign The blood Wassermann was positive The examination of the cerebrospinal fluid showed pressure of 130 mm There were no cells, the globulin test was negative, colloidal gold reaction was 1223310000 and the Wassermann test was negative

Three cases were followed for periods varying from six months to two years Two of the cases were clinically symptom-free In 1 case (no 8) followed for one year, the final serological status was not known In case 16, followed for one year, the cerebrospinal fluid was normal Case 9, which was followed for nine months, showed clinical and serological improvement

Group II   Acute syphilitic meningitis of the vertex (20 cases)

In this group there were 20 cases which presented in addition to the signs and symptoms of acute hydrocephalus, i e , headache, vomiting,

CASE NUMBERS	Initials	Age	Sex	Time after infection	Previous treatment	Duration of symptoms	Headache, nausea and vomiting	Convulsions	Mental disturbance and delirium	Stiff neck and Kernigs' sign	Choked disc	NEUROLOG
27	J M	29	M	3 mos	None	1 wk	+	0	+	+	+	
28	T H	30	M	3 mos	None	?	+	0	0	0	−	Right plegi
29	C B	19	F	4 mos	Sub standard	2 wks	+	+	0	+	−	
30	F C	26	M	4 mos	Sub standard	3 wks	+	+	0	+	0	
31	A Γ	21	Γ	6 mos	Sub-standard	4 wks	+	+	0	0	−	
32	M R	23	M	9 mos	Sub standard	3 wks	+	+	0	+	+	Right VIII, VI, V
33	A F	26	M	10 mos	Standard	1 wk	+	+	0	+	0	
34	A D	28	M	10 mos	Sub-standard	1 mo	+	+	0	0	+	
35	R H	28	M	1 yr	Sub-standard	3 mos	+	0	+	+	+	Left he
36	P C	31	M	15 mos	Sub-standard	2 wks	+	+	+	+	+	
37	C B	31	F	17 mos	Sub-standard	2 wks	+	+	+	0	+	Left II
38	H R	23	F	5 yrs	None	3 wks	+	+	+	0	+	
39	C W	37	M	15 yrs	Sub standard	2 mos	+	0	+	0	0	
40	Ε C	31	Γ	15 yrs	Sub standard	7 mos	+	0	0	+	+	Left he
41	M D	42	F	26 yrs	Sub-standard	2 wks	+	0	+	+	−	Tabes
42	H H	30	M	?	None	1 wk	+	+	+	0	−	
43	J M	33	M	?	None	6 mos	+	+	0	0	0	Transie sia
44	J Q	38	M	?	None	?	+	+	+	+	−	
45	B P	38	F	?	Sub standard	1 wk	+	+	+	+	+	
46	D B	46	F	?	Sub-standard	3 wks	+	+	+	0	+	
High		46		26 yrs		28 wks						
Low		19		3 mos		1 wk						
Mean		30				6 wks						

* Convulsions persisted
† Subsequently positive

and choked discs, signs and symptoms of a localization of the meningitis over the vertex of the brain, as evidenced by the occurrence of

convulsions, focal symptoms such as hemiplegia and aphasia, and mental symptoms Table 2 presents a summary of these cases

Sex and age distribution The sex distribution in this group was

			TA AND CEREBROSPINAL FLUID FINDINGS AT FIRST LUMBAR PUNCTURE					FOLLOW UP			
Cells per cu mm	Per cent of polymorphonuclear leucocytes	Globulin reaction	Total protein (mgm per 100 cc.)	Colloidal gold curve	Sugar (mgm per 100 cc.)	Chlorides (mgm per 100 cc)	Cerebrospinal fluid Wassermann reaction	Period followed	Treatment	Clinical results	Final serological status
350	70	−					Positive	5 mos	Sub-standard	Improved	Unknown
700	10	++		5555441100			Positive	1 mo	Sub-standard	Improved	Unknown
800		+					Positive	1 yr	Sub-standard	Recovered	Unknown
45	36	++	105	1223100000	83	711	Positive	6 mos	Sub-standard	Recovered	Normal
43	0	+		5555554200			Positive	11 yrs	Standard	Recovered*	Normal
1 170	50	++	381	1123321000			Positive	21 mos	Standard	Recovered	Normal
1 172	10	+	83	1112110000			Positive	2 yrs	Standard	Recovered	Normal
690	10	+					Negative†	2 yrs	Standard	Recovered	Improved
630		++	100	5335443210	46	697	Positive	1 mo	Sub-standard	Improved	Unchanged
109		+	54	5555543210	52	702	Positive	8 mos	Standard	Improved	Unknown
160	0	++		1233210000			Positive	5 yrs	Standard	Recovered	Normal
347	0	+	132	0011233111	32	658	Negative	1 wk	Sub-standard	Improved	Unknown
238	6	−					Positive	2 yrs.	Standard	Recovered	Normal
110	0	++	160	4454443332	35	687	Positive	1 yr	Sub-standard	Improved	Unknown
680	80	+	78	1122231200	69	680	Negative†	1 mo	Sub-standard	Improved	Improved
660	4	++	222	1223320000	30		Positive	6 yrs	Standard	Recovered	Normal
117	0	++	192	0001222222			Positive	2 yrs	Standard	Recovered	Normal
195	0	+	49		84	728	Positive	1 mo	Sub-standard	Improved	Unknown
52	0	+	93	0002332100			Positive	2 yrs	Standard	Recovered	Unknown
23	0	+	54	0000000000	59	733	Negative	30 mos	Standard	Recovered	Normal
1 172	80		381		84	733					
23	0		49		30	658					
415	16		130		54	700					

very similar to that in the first group, that is, there were 12 males and 8 females The age distribution was also very similar The ages

varied between 19 and 46 years, with the majority (90 per cent) between the ages of 19 and 39 years

Time of onset of the meningitis In 15 cases the time of the primary infection was known In 5 cases (25 per cent) the meningitis was the first symptomatic evidence of the syphilitic infection This is almost exactly equal to the incidence of such cases in the first group (27 per cent) In the 15 cases in which the time of infection was known, the interval between the initial infection and the onset of the meningitis varied between three months and twenty-six years In 9 of the 15 cases (60 per cent) the meningitis occurred within one year of the primary infection The remaining 6 cases occurred two, two, seven, fifteen, fifteen, and twenty-six years respectively, after the primary infection Although the early cases are greatly in the predominance in this group, there is a higher percentage of late cases in this group than in Group I There was a history of a secondary rash in 9 cases (45 per cent) This is exactly the same as in the first group In 3 of the cases, the rash was present on admission to the hospital with the meningitis

Previous treatment In 6 cases (30 per cent) there was no history of any previous anti-luetic therapy This percentage is the same as that in the first group In all the remaining cases the meningitis developed after a lapse in treatment varying from three weeks to several years *None of the cases of vertical meningitis developed while the patients were under active treatment* Eleven cases developed symptoms after a lapse from arsenical therapy, either alone or in combination with mercury In three cases symptoms developed after a lapse in arsenical and bismuth therapy, and in 1 case after a lapse in bismuth therapy alone The occurrence of the meningitis in the 6 cases without any therapy and in the case which was treated with bismuth alone, indicate (as did the 8 cases in Group I) that the arsenical therapy has no direct relationship to the onset of the meningitis

Symptoms The symptoms in these cases which caused the patients to seek admission to the hospital were of two types

(1) Headaches, nausea, and vomiting indicating an increased intracranial pressure

(2) Convulsions, mental confusion, delirium, hemiplegia and aphasia indicating a localized involvement of the inflammatory process in the meninges over the vertex of the brain

The occurrence of these two types of symptoms in these cases indicates that the meningeal involvement was more widespread in these cases than in those of the first group   This is also evidenced by the fact that 2 of the cases also had cranial nerve palsies indicating involvement of the meninges at the base

The symptoms of acute hydrocephalus, that is, headaches, nausea and vomiting, which were present in all cases before admittance to the hospital, varied in duration from one week to seven months   In the majority of cases (80 per cent) the symptoms were of less than one month's duration   There were, however, more cases in this group with a relatively long duration of symptoms than in Group I   In 2 cases (nos 40 and 43) severe headaches had been present for more than six months   Case 40 was admitted to the hospital after the sudden onset of a left hemiplegia   Case 43 had severe headaches for six months with *petit mal* attacks and transient attacks of aphasia

Convulsive phenomena were present in 14 cases   In 4 cases this consisted of attacks of loss of consciousness which were not further described   In 2 cases the attacks were typical *grand mal* convulsions   Two of these cases were admitted in status epilepticus   Jacksonian convulsive attacks were not noted in any of our cases but they have been recorded in the literature   *Focal symptoms* were present in 4 cases   Three cases were admitted after the sudden onset of a hemiplegia—a right hemiplegia in case 28 and a left hemiplegia in cases 35 and 40   Case 43 had numerous attacks of *aphasia* which were of only a few minutes duration   *Mental symptoms* such as delirium mental confusion, and stupor, were present in eleven cases

Neurologic signs   Evidence of meningeal irritation was present in 11 of the 20 cases (55 per cent) as compared with 90 per cent in Group I   The pupillary reactions to light and on convergence were normal in all cases except case 41, which was a case of tabes dorsalis, and cases 32 and 37, each of which had paralysis of the third cranial nerve   In several cases the pupils were recorded as being irregular in outline   The pupillary findings in this group were similar to those in Group I

Cranial nerve palsies were present in case 32 (left third and bilateral sixth and eighth nerves) and case 37 (left third and sixth nerves)   Both of these cases also had convulsions   The occurrence of convulsions together with cranial nerve palsies indicates that the meningitis was widespread in these cases

varied between 19 and 46 years, with the majority (90 per cent) between the ages of 19 and 39 years

Time of onset of the meningitis   In 15 cases the time of the primary infection was known   In 5 cases (25 per cent) the meningitis was the first symptomatic evidence of the syphilitic infection   This is almost exactly equal to the incidence of such cases in the first group (27 per cent)   In the 15 cases in which the time of infection was known, the interval between the initial infection and the onset of the meningitis varied between three months and twenty-six years   In 9 of the 15 cases (60 per cent) the meningitis occurred within one year of the primary infection   The remaining 6 cases occurred two, two, seven, fifteen, fifteen, and twenty-six years respectively, after the primary infection   Although the early cases are greatly in the predominance in this group, there is a higher percentage of late cases in this group than in Group I   There was a history of a secondary rash in 9 cases (45 per cent)   This is exactly the same as in the first group   In 3 of the cases, the rash was present on admission to the hospital with the meningitis

Previous treatment   In 6 cases (30 per cent) there was no history of any previous anti-luetic therapy.   This percentage is the same as that in the first group   In all the remaining cases the meningitis developed after a lapse in treatment varying from three weeks to several years   *None of the cases of vertical meningitis developed while the patients were under active treatment*   Eleven cases developed symptoms after a lapse from arsenical therapy, either alone or in combination with mercury.   In three cases symptoms developed after a lapse in arsenical and bismuth therapy, and in 1 case after a lapse in bismuth therapy alone   The occurrence of the meningitis in the 6 cases without any therapy and in the case which was treated with bismuth alone, indicate (as did the 8 cases in Group I) that the arsenical therapy has no direct relationship to the onset of the meningitis

Symptoms   The symptoms in these cases which caused the patients to seek admission to the hospital were of two types

(1) Headaches, nausea, and vomiting indicating an increased intracranial pressure.

(2) Convulsions, mental confusion, delirium, hemiplegia and aphasia indicating a localized involvement of the inflammatory process in the meninges over the vertex of the brain

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Convulsive phenomena were present in 14 cases   In 4 cases this consisted of attacks of loss of consciousness which were not further described   In 2 cases the attacks were typical *grand mal* convulsions Two of these cases were admitted in status epilepticus   Jacksonian convulsive attacks were not noted in any of our cases but they have been recorded in the literature   *Focal symptoms* were present in 4 cases   Three cases were admitted after the sudden onset of a hemiplegia—a right hemiplegia in case 28 and a left hemiplegia in cases 35 and 40   Case 43 had numerous attacks of *aphasia* which were of only a few minutes duration   *Mental symptoms* such as delirium mental confusion, and stupor, were present in eleven cases

Neurologic signs   Evidence of meningeal irritation was present in 11 of the 20 cases (55 per cent) as compared with 90 per cent in Group I   The pupillary reactions to light and on convergence were normal in all cases except case 41, which was a case of tabes dorsalis, and cases 32 and 37, each of which had paralysis of the third cranial nerve   In several cases the pupils were recorded as being irregular in outline The pupillary findings in this group were similar to those in Group I

Cranial nerve palsies were present in case 32 (left third and bilateral sixth and eighth nerves) and case 37 (left third and sixth nerves) Both of these cases also had convulsions   The occurrence of convulsions together with cranial nerve palsies indicates that the meningitis was widespread in these cases

The examination of the fundi was recorded in 13 of the 20 cases, and choked discs were present in 8 cases (62 per cent) which is only slightly less than the number found in Group I (73 per cent).

The deep reflexes were generally increased in 8 cases and unilaterally increased in 3 cases with a hemiplegia   In the latter 3, Babinski's toe sign was present on the paralyzed side   This is in contrast to the findings in Group I, where no definite evidence of pyramidal tract involvement was observed

Serology   The serological findings in these cases at the time of admission to the hospital are shown in table 2   The blood Wassermann was recorded in 17 cases   It was positive in 10 cases (59 per cent) and negative in 7 cases (41 per cent)   The percentage of negative blood Wassermann reactions in this group is slightly higher than in the first group (30 per cent)   This is further evidence of the unreliability of the blood Wassermann test in these cases   The cerebrospinal fluid Wassermann reaction was positive in 16 cases (80 per cent) and negative in 4 cases (20 per cent)   Evidence of other abnormalities such as a pleocytosis, increased protein, or an abnormal gold curve, was present in the cerebrospinal fluid of these cases, but due to their unusual nature, a brief summary of these cases is given below

Case 34   A D , a 28-year old white male was admitted to the hospital June 28, 1928. Ten months previously he had a penile chancre   In August, 1927, he received six intravenous injections of an arsenical drug, and lapsed from treatment until March, 1928, when he returned complaining of headache   He was given one intramuscular injection of bismuth   He again lapsed from treatment and one month before entry began to complain of headaches, nausea, and vomiting, and to have several *petit mal* attacks   The examination on admission to the hospital with the meningitis, showed a mild choking of the optic discs and increased deep reflexes   The blood Wassermann was negative   The lumbar puncture showed a pressure of 130 mm spinal fluid   The fluid contained 690 lymphocytes per cubic millimeter, the globulin test was positive and total protein was 83 mgm per 100 cc   The colloidal gold curve was 1112110000   The spinal fluid Wassermann was negative   The patient was punctured ten days later   The cerebrospinal fluid showed findings similar to those at first puncture, except that now the cerebrospinal fluid Wassermann reaction was positive and the blood Hinton test was positive   Three subsequent punctures also showed a positive Wassermann reaction in the spinal fluid   The patient was

treated continuously for twenty-six months with neo-arsphenamin, intra-spinous therapy, and tryparsamide, at the end of which time he was clini-cally recovered   The blood Wassermann tests were negative, but the cerebrospinal-fluid showed 2 lymphocytes and a weakly positive Wasser-mann reaction on one examination, and on repeated examinations a few months later, it contained 42 lymphocytes per cubic millimeter, and showed a negative Wassermann reaction   The patient was then lost to the clinic Over a period of twenty-six months this patient received twenty injections of neo-arsphenamin totalling 9 grams, thirty-five injections of iodo quinine of bismuth, one arsphenamin injection, of 0 3 gram, and seven intraspinous treatments after the method of Swift-Ellis

Case 38   H R , a 23-year old white female, was admitted to the hospital March 3, 1931   Five years previously she had a secondary rash and had four miscarriages in the next two years   She claimed to have received some treatment in the first two years of her infection   The exact amount was not known   Two and a half years previously she came to the clinic and a positive blood Wassermann was found, but she did not return for treatment On admission to the hospital in March, 1931, she complained of severe headaches, nausea, and vomiting, that had been present for three weeks The day before admission she had a convulsive attack and was unconscious for five hours   On examination, the patient was slightly stuporous, the pupils were irregular, both optic discs were choked, the deep reflexes were increased and there was bilateral Babinski sign   The blood Wassermann was positive   The cerebrospinal fluid was under a pressure of 190 mm The fluid contained 347 lymphocytes, the globulin test was positive, the total protein was 132 mgm , sugar 32 mgm , and chlorides 658 mgm per 100 cc   The colloidal gold test was 0011233111 and the cerebrospinal Wassermann was negative   The patient refused treatment, left the hospital against advice, and was lost to the clinic

Case 41   M D , a 42-year old white female was admitted to the hospital February 10, 1929   She had a primary lesion followed by skin rash at the age of sixteen   She received no treatment at the time of the initial infection, and had received only six intravenous treatments in the intervening years On admission to the hospital she was in a delirious state and was unable to give any history, but it was learned that she had been suffering from nausea and vomiting for four weeks   Her speech was somewhat thick, there was stiffness of the neck, and Kernig's sign was present   The pupils were irregular and reacted sluggishly to light   The knee and ankle jerks

were absent   The blood Wassermann was negative   A lumbar puncture showed an initial pressure of 400 mm   The fluid contained 680 white blood cells (80 per cent polymorphonuclear leucocytes)   The globulin reaction was positive, the total protein was 78 mgm , sugar 69 mgm   chlorides 680 mgm   per 100 cc   The colloidal gold curve was 1122232222 and the cerebrospinal fluid Wassermann was negative   A lumbar puncture done the following day showed similar findings with a negative Wassermann reaction   Lumbar punctures three and ten days respectively after the first lumbar puncture showed a weakly positive Wassermann reaction   The patient remained in the hospital one month   During this time she was treated by intravenous injections of neosalvarsan, intramuscular injections of bismuth, and repeated lumbar punctures   Her mental state cleared and the cerebrospinal fluid pressure returned to normal   She was discharged to the out-patient clinic with the diagnosis of tabes dorsalis and acute syphilitic meningitis   She did not return for treatment and was lost to the clinic

Case 46   D. B , a 46-year old colored female was admitted to the hospital June 10, 1931   She had no knowledge of a primary sore or secondary rash   She was first seen in another clinic (at which her husband was receiving treatment for syphilis) three years previous to the onset of her meningitis   At this time her blood Wassermann was positive   She was given eleven injections of an arsenical drug, and nineteen injections of bismuth   The last treatment was two months before entry, at which time her blood Wassermann was positive   On admission to the hospital she complained of headache, nausea and vomiting of three weeks duration, and vague visual disturbances   She was slightly confused mentally, and had a *grand mal* convulsion shortly after admission   The optic discs were blurred, the deep reflexes were hyperactive, with unsustained ankle clonus   The blood Wassermann test was negative   The cerebrospinal fluid was under pressure of 170 mm and contained 23 lymphocytes per cubic millimeter.   The globulin test was negative and protein content was 54 mgm per 100 cc , the colloidal gold test and the cerebrospinal fluid Wassermann were negative.   The patient was treated by intravenous injections of neosalvarsan, intramuscular injections of bismuth, and repeated lumbar punctures   The blood Wassermann became positive while the patient was under treatment but the cerebrospinal fluid Wassermann remained negative, although the colloidal gold test was 0123321000 on two occasions   She remained in the hospital one month and was discharged symptom-free   She was treated irregularly in the out-patient department for eleven months,

receiving six injections of neoarsephenamin and five injections of bismuth At the end of this time she was symptom-free and the blood Wassermann was negative   Re-examination of the cerebrospinal fluid was not obtained

Treatment and results   The patients in this group as well as in the first group, received various forms of therapy   All of the cases received repeated lumbar punctures and intravenous injections of an arsenical drug while in the hospital   Some of the cases also received intramuscular injections of mercury or bismuth   Six cases received intraspinous injections after the method of Swift-Ellis   Regardless of the type of therapy, all of the cases, with the exception of case 38 which left the hospital against advice, were discharged from the hospital relieved of their presenting symptoms   The average duration of stay in the hospital was 23 days   After discharge from the hospital, 9 cases were followed for periods varying from two to eleven years   The final serological status was determined in 8 of these 9 cases   Six cases followed for periods varying from two to five years, were clinically recovered and were serologically normal at the end of the period of observation   Case 31, which was followed for eleven years, was serologically normal at the end of this period and was regarded as clinically recovered with the exception of the fact that she continued to have occasional convulsive seizures   These seizures were not considered as indicating continued activity of the syphilitic infection in the nervous system but were thought to be the result of a meningeal scar

Case 34 followed for two years with continuous treatment, was symptom-free at the end of this period   The neurological examination was negative but the cerebrospinal fluid contained 42 lymphocytes and had a positive globulin test   The colloidal gold and Wassermann tests were negative

Case 45 was followed for two years   At the end of this time she was clinically recovered but the final serological status was not known

Five cases were followed for periods varying from six months to two years   In two instances (cases 30 and 32) the patients were symptom free and the cerebrospinal fluid was normal   In the 3 remaining cases (nos 29, 36, and 40) the patients were clinically symptom-free but the final serological status was unknown

Group III (basilar type)   Acute syphilitic meningitis of the base of the brain (34 cases)

Cranial nerve palsies indicating involvement of the meninges at the base of the brain were found in 34 cases   Evidence that the meningitis was not confined to the base of the brain in these cases was shown by the fact that signs and symptoms of acute hydrocephalus in the form of headache, vomiting, and choked discs were present in a considerable number of these cases   No cases which showed convulsive phenomena, focal signs, or mental symptoms were included in this group

Sex and age incidence   This group is much larger than either of the other two, and it is interesting to note that the sex incidence (19 males and 15 females) in this group is much more nearly equal than was true in Groups I and II

The age incidence varied between 17 and 56 years   The youngest was a congenital syphilitic aged 17.   The majority of the patients (77 per cent) were between 19 and 39 years old   This percentage is somewhat less than in the two previous groups   Also in this group there were 4 cases over 50 years of age, whereas only 1 case over 50 years of age was found in Group I, and none in Group II   The number of patients over 50 years of age in this group is probably accounted for by the fact that the onset of basilar meningitis more often occurs ten to twenty years after the initial infection than does acute syphilitic hydrocephalus or syphilitic vertical meningitis   It is of importance to note that none of our cases were more than sixty years of age   We have not seen the report of any such case in the literature

Time after the initial infection   The time after the initial infection was known in 25 cases   In 9 cases (26 per cent) the meningitis was the first symptomatic evidence of the syphilitic infection   This percentage is exactly similar to that in the previous two groups   In the 24 cases in which the time of infection was known, the period from the initial infection to the appearance of symptoms varied from two months to twenty years   In 13 of these cases (54 per cent) the meningeal symptoms developed within one year of the initial infection While this indicates that basilar meningitis is predominantly a manifestation of early syphilis, the percentage is very much less than in Group I (95 per cent), and considerably less than in Group II (73 per

cent) A history of a secondary rash was present in 11 of the 34 cases (32 per cent) This is slightly less than in the previous two groups (46 and 45 per cent respectively) In 3 cases (nos 52, 56, and 76) the rash was present along with the meningitis at the time of admission to the hospital

Previous treatment Fifteen of the 34 cases (44 per cent) had received no anti-luetic therapy prior to the onset of the meningitis This is somewhat higher than the percentage of untreated cases (30 per cent) in Groups I and II Six cases had received previous arsenical therapy, 8 cases arsenical and mercury therapy, 4 cases arsenical and bismuth therapy, and 1 case bismuth therapy alone *In all but 2 of the cases that had received anti-luetic treatment prior to the onset of the meningitis, the symptoms developed during a lapse from treatment varying in length from three weeks to many years* In case 11, the symptoms developed while the patient was receiving mercury therapy This patient had a secondary rash in January, 1929 and was given ten weeks intravenous injections of neosalvarsan, followed by weekly injections of mercury The symptoms developed during the course of the mercury therapy, and the patient was admitted to the hospital June 25, 1929

Case 12 developed symptoms while receiving intramuscular injections of mercury This patient had a primary sore seven months, and a secondary rash five months before the onset of the meningitis At the time of the secondary rash, he was given two intravenous injections of diarsenol, and for the six weeks previous to entry to the hospital, he was given intramuscular injections of mercury twice a week

The development of the meningeal symptoms in patients while receiving mercury therapy is not rare Several such cases were reported by Moore (1929)

Symptoms The symptoms that were present in the basilar group can be divided into two types

(1) General symptoms of increased intracranial pressure or acute hydrocephalus, i e , headaches, nausea and vomiting

(2) Symptoms of cranial nerve palsies indicating involvement of the basilar meninges

The duration of symptoms before admission to the hospital varied quite markedly in this group, i e , from one week to nine months In

the majority of the patients (60 per cent) the symptoms were of less than one month's duration but there were many more cases in this group with symptoms of longer duration than in the previous groups. This is perhaps related to the fact that the general symptoms of headache, nausea and vomiting were less severe in this group and also to the fact that the markedly incapacitating symptoms such as mental disturbances, convulsions, hemiplegias, and aphasia were absent, and the patients did not feel the necessity of hospital care

The general symptoms of increased intracranial pressure were present in 27 of the 34 cases (79 per cent) This is much less than the 100 per cent incidence of these symptoms in the cases of the previous two groups, and also these symptoms were, as a rule, much less severe in this group

Symptoms of cranial nerve palsies were present in all of the cases and were related to the nerves involved In some of the cases the patients were not aware of a mild fifth or seventh cranial nerve weakness, or a loss of hearing in one ear.

Neurologic signs. Evidences of meningeal irritation, i e , stiffness of the neck and Kernig's sign, were present in only 13 cases (36 per cent) This is a much lower percentage than was present in Groups I and II (85 and 55 per cent respectively).

The pupillary reactions to light and on convergence were interfered with more often in this group of cases than in the other two groups This was largely due to two factors· (1) the meningitis occurred in a number of these patients five to twenty years after the initial infection, which is ample time for the development of pupillary abnormalities, and (2) the occurrence of third nerve paralyses in 10 cases In all of the patients with paralysis of the third nerve, the pupil of the involved eye was dilated and fixed to light and accommodation, with the exception of case 68, in which the paralysis of the third nerve involved only the external muscles In addition, the pupils were irregular in 8 cases, and in 3 of these cases the light reaction was very sluggish or absent In case 69, a congenital luetic with marked optic atrophy, the pupils were large, and did not react to light

The fundi were examined in 33 cases and choked disc was present in 14 cases (41 per cent) This is much less than in the other two groups (73 and 62 per cent respectively)

Cranial nerve palsies The cranial nerves were unilaterally involved in 22 cases (right side ten, left side twelve) Bilateral involvement was found in 12 cases A single nerve was involved in 6 cases, a pair in 5 cases, two different nerves in 10 cases, three nerves in 9 cases, and more than three nerves in 4 cases An analysis of these paralyses follows

First nerve None of the patients had subjective complaints with reference to the sense of smell, and in most cases tests of olfactory nerve function were inadequate

Second nerve In 6 cases the impairment of visual acuity was in excess of the amount that might be explained on the basis of increased intracranial pressure and was considered to be evidence of active involvement of the optic nerves In all cases which showed involvement of the optic nerve, the involvement was bilateral

Third, fourth, and sixth nerves The third, fourth, and sixth nerves were involved in 10, 1, and 7 cases respectively The sixth nerve was involved on both sides in 2 cases There was no instance of bilateral involvement of the third or fourth nerves

Fifth nerve There was unilateral involvement of the fifth nerve in 7 cases (right three, left four), and bilateral involvement in 1 case The motor and sensory function of the fifth nerve was impaired in 4 cases, the motor function alone in 2 cases, and the sensory function alone in 1 case

Seventh nerve The seventh nerve was unilaterally involved in 16 cases (right eight, left eight), and bilaterally involved in 2 cases

Eighth nerve The eighth nerve was involved in 13 cases, unilateral in 10 cases (right six, left four) and bilateral in 3 cases The acoustic division was involved alone in 8 cases, the vestibular alone in 4 cases, and combined involvement was present in 1 case Since audiometric tests were not performed in these cases, it is very probable that impairment of hearing was present in all of the cases with involvement of the eighth nerve Moore (1929) did not find isolated involvement of the vestibular branch in any of his cases

Ninth and tenth nerves Difficulty in talking and swallowing indicating involvement of the ninth and tenth nerves, was present in 5 cases On examination the weakness of the palate was bilateral in 1 case, and unilateral in 4 cases (right two, left two)

Eleventh nerve   There was no record of involvement of the eleventh nerve in any case

Twelfth nerve   Involvement of the twelfth nerve, as evidenced by weakness or paralysis of muscles of one side of the tongue, was shown in 3 cases (right two, left one)   There was no case with bilateral involvement of the twelfth nerve

Reflexes   There were no pathological reflexes indicating focal involvement, but in 8 cases the reflexes were very lively, possibly indicating pyramidal tract irritation   In case 62, the knee and ankle jerks were absent on admission but returned in a few days   In case 63, the knee and ankle jerks were absent on the right side

Serology   The serological findings in these 34 patients on admission to the hospital are given in table 3, and are discussed more fully later The blood Wassermann reaction was recorded in 32 cases, positive in 22 (69 per cent) and negative in 10 (31 per cent)   The cerebrospinal fluid Wassermann was positive in 30 cases (88 per cent) and negative in 4 cases (12 per cent)   All of the 4 cases with negative cerebrospinal fluid Wassermann reactions had very definite abnormalities in the cerebrospinal fluid, i e , pleocytosis, increased protein and abnormal colloidal gold curves, indicating an active meningitis   On account of their interest a brief summary of these cases is presented below.

Case 60   A T , a 30-year old white female was admitted to the hospital December 16, 1925   She had had a primary lesion two years before admission, followed by a secondary rash and positive blood serology   She was treated at that time with five injections of neoarsphenamin with reversal of the blood Wassermann reaction.   One month before entry to the hospital she noticed that objects appeared double and that her right eye-lid drooped Examination on admission showed only stiffness of the neck and paralysis of the right third and left fourth nerves   The blood Wassermann test was negative   The cerebrospinal fluid showed 120 cells per cubic millimeter, a positive globulin reaction, a protein content of 98 mgm per 100 cc and a colloidal gold reaction of 0001122110   The fluid contained 39 mgm of sugar per 100 cc , and the Wassermann reaction was negative   She was treated in the hospital intraspinously, by the method of Swift-Ellis, with improvement and was followed in the out-patient department for three years   The third nerve palsy persisted, and optic atrophy developed in the right eye   At the end of this time the blood Wassermann was negative and the cerebrospinal fluid was normal except that the gold curve was 4422211100.

Case 64 A L , a 34-year old white male was admitted to the hospital December 18, 1917 He had had a penile chancre four years previously but there had been no secondary rash and he had not received any anti-luetic therapy Three weeks before entry he had complained of generalized pains and paralysis of the left half of the face, and a drooping of the left lid developed Examination on admission showed paralyses of the left seventh, ninth, and tenth nerves The blood Wassermann reaction was positive The cerebrospinal fluid contained 70 cells per cubic millimeter, the globulin test was *2 plus*, the colloidal gold reaction 3332100000 and the cerebrospinal fluid Wassermann reaction was negative He was treated in the hospital by the Swift-Ellis method and was followed in the out-patient department for fifteen years with active treatment continuously for the first two years and one course of arsphenamin each year for the three years following At the end of this period the patient was symptom-free The blood Wassermann reaction was negative, and the cerebrospinal fluid was entirely normal Two years after the attack of meningitis, the cerebrospinal fluid Wassermann was positive on several occasions

Case 71 A S , a 56-year old male was admitted to the hospital May 15, 1931 He had a primary sore twenty years previous to entry to the hos-pital, with only local treatment There was no history of a secondary rash One month before entry the patient noticed a weakness of the right side of his face On entry the examination showed unequal, irregular pupils that did not react to light There was a palsy of the right seventh and a paresis of the right fifth cranial nerves Blood Wassermann and Kahn tests were positive The cerebrospinal fluid was under a pressure of 160 mm The fluid contained 20 lymphocytes per cubic millimeter, the globulin reaction was positive, total protein content was 43 mgm , and the colloidal gold and Wassermann reactions were negative The patient was treated in the out-patient department with tryparsamide, and bismuth, continuously for two years At the end of this period the patient's blood Kahn reaction was still positive, but reexamination of the cerebrospinal fluid was not permitted

Case 76 B L , a 30-year old white female was admitted to the hospital September 4, 1928, with a history of headache and vomiting for five weeks, and tinnitus and ataxia for two weeks There was no history of primary sore or previous treatment On admission a secondary rash was present (? recurrent secondaries) On examination on admission to the hospital she showed choked discs, nystagmus, and a slightly impaired light reaction of the pupils X-ray of the skull showed a syphilitic osteomyelitis of the

				HISTORY OF CASES			SYMPTOMS			NEUROLOGIC SIGNS
CASE NUMBERS	Initials	Age	Sex	Time after infection	Previous treatment	Duration of symptoms	Headache, nausea and vomiting	Stiff neck and Kernig's sign	Choked disc	Cranial nerve palsies
47	H D	18	F	2 mos	Sub-standard	1 mo	+	0	+	Right II, III, VI, V left II, VI
48	D M	28	M	2 mos	Sub standard	2 wks	+	+	+	Right V, VII, XII, III
49	B C	43	M	3 mos	Sub standard	3 wks	+	0	0	Right VIII, left VIII
50	H W	19	F	4 mos	None	1 mo	+	+	+	Right V, VII, left V, VIII
51	M B	26	F	4 mos	Standard	3 wks	+	0	+	Right II, VI, left II, VII
52	M R	33	F	4 mos	Sub-standard	1 mo	+	0	+	Left VII, VIII
53	M A	22	F	5 mos	Sub-standard	2 wks	+	0	0	Right VI, VII, VIII
54	F H	19	M	5 mos	Sub-standard	2 wks	0	+	0	Right VII, left VII
55	G P	22	M	5 mos	Sub-standard	2 wks	+	+	0	Light VII
56	H M	18	M	6 mos	Sub standard	1 mo	+	+	+	Right II, III, VI, left
57	M G	29	F	6 mos	Sub-standard	3 mos	+	+	+	Left V, VII, VIII
58	B S	22	M	7 mos	Sub-standard	5 wks	+	0	0	Left VII
59	J S	26	M	1 yr	Sub standard	2 mos	+	+	+	Right VII, VIII
60	A T	30	F	2 yrs	Sub standard	1 mo	+	+	0	Right III, IV, left VI
61	A H	55	M	3 yrs	None	3 wks	+	0	0	Right VII, VIII
62	W H	27	F	3 yrs	Sub-standard	3 wks	+	+	+	Right II, left II
63	A K	43	F	4 yrs	Sub-standard	2 mos	+	0	+	Left X, XII
64	A L	34	M	4 yrs	None	3 wks	0	0	0	Left VII, IX, X
65	M R	27	M	8 yrs	Sub-standard	5 wks	0	0	0	Left V, VII, VIII
66	K E	40	M	12 yrs	Sub standard	10 wks	0	0	0	Right III, VII, VIII
67	C H	38	M	15 yrs	None	6 wks	+	0	+	Right II, left II
68	R F	38	M	16 yrs	Standard	2 wks	+	+	0	Pupils abnormal, left VI
69	E C	17	F	Congenital	Sub-standard	9 mos	+	0	0	Right X, XII, optic atrophy, left X
70	E E	39	F	20 yrs	None	8 mos	0	0	—	Right III, V
71	A S	56	M	20 yrs	None	1 mo	0	0	0	Pupils abnormal, right VII
72	S F	21	M	?	None	3 wks	+	+	0	Right III
73	N T	21	F	?	None	2 wks	+	+	0	Left V
74	C G	28	M	?	None	1½ mos	+	0	+	Right II, VI, VII, VIII, X, left II, VI
75	M Z	30	M	?	None	3 wks	0	+	0	Left III, VII
76	B L	30	F	?	None	5 wks	+	0	+	Pupils abnormal, right VIII, left VIII
77	W H	37	M	?	None	4 mos	0	0	0	Pupils abnormal, left
78	W T	43	M	?	None	1 wk	+	0	0	Left III
79	F B	50	F	?	None	10 days	+	0	0	Right VIII, X
80	J D	51	F	?	None	9 mos	+	0	+	Pupils abnormal, right VIII, left VII, VIII

nuclear leucocytes	Globulin reaction	Total protein (mgm per 100 cc.)	Colloidal gold curve	Sugar (mgm per 100 cc.)	Chlorides (mgm per 100cc)	Cerebrospinal fluid Wassermann reaction	Period followed	Treatment	Clinical results	Final serological status
0		44	1223210000			Positive	2 yrs	Sub-standard	Improved	Unknown
	++	85	0012231000			Positive	6 yrs	Sub standard	Improved	Remained abnormal
	++	161	5555432100			Positive	2 yrs	Standard	Recovered	Unknown
4	+					Positive	3 yrs	Standard	Recovered	Normal
	−					Positive	1 mo	Sub standard	Improved	Unknown
	+	57	4332100000			Positive	7 yrs	Standard	Recovered	Normal
	+	128	3222222100	47		Positive	2 yrs	Standard	Recovered	Normal
	+	53	1112221111	53		Positive	8 mos	Standard	Improved	Improved
	+	236	5555543210	34	667	Positive	2 mos	Standard	Improved	Improved
10	−					Positive	15 yrs	Standard	Advanced to dementia paralytica	' Paretic formula
	++	130	5543210000	35	742	Positive	1 mo	Sub-standard	Improved	Very slightly improved
10	++	100	5555432100			Positive	11 yrs	Standard	Recovered	Normal
16	++					Positive	1 mo	Sub-standard	Improved	Improved
	+	98	0001122110	39		Negative	3 yrs	Standard	Advanced	Improved
	+					Positive	6 wks	Sub standard	Improved	Unknown
	++	111	0000123210			Weakly positive	1 mo	Sub-standard	Improved	Improved
	+		3332100000			Positive	2 yrs	Sub-standard	Died	Unknown
	++					Negative	15 yrs	Standard	Recovered	Normal
	++	177	0012321000			Positive	3 mos	Sub-standard	Improved	Unknown
	+	133	2234333220			Positive	9 mos.	Standard	Improved	Unknown
	+	133	4555553211	40		Positive	4 days	None	Died post operationem	
5	+		5555331000			Positive	4 yrs	Standard	Developed dementia paralytica	Unchanged
	+	68	0122321000	34	670	Positive	1 yr	Standard	Improved	Unknown
20	++	85	5553210000	80		Positive	4 yrs	Standard	Recovered†	Normal
0	+	43	0000000000			Negative	2 yrs	Standard	Recovered	Unknown
	−		3555555410			Positive	1 mo	Sub-standard	Improved	Unknown
24	+					Positive	1 yr	Standard	Recovered	Unknown
1	++	121	5555432100			Positive	4 yrs	Standard	Recovered	Normal
0	−					Positive	3 yrs	Standard	Recovered	Improved
	0	27	5555432100			Negative	3 yrs	Standard	Recovered	Normal
0	++	105	2223332110			Positive	9 mos	Sub-standard	Improved	Unknown
0	+					Positive	3 wks	Sub-standard	Improved	Unknown
0	++	67	2222333221			Positive	2 mos	Sub-standard	Improved	Unknown
20	++	105	2223311000	18	662	Positive	3 wks.	Sub-standard	Improved	Unknown
24		236		80	742					
		27		18	662					
9		103		42	685					

frontal bone   The blood Wassermann was positive   The cerebrospinal fluid showed 30 lymphocytes per cubic millimeter, a negative globulin reaction, and a total protein content of 27 mgm per 100 cc   The colloidal gold reaction was 5555543210, and the cerebrospinal fluid Wassermann was negative   The patient was treated in the hospital by the intraspinous method of Swift-Ellis, and actively treated in the out-patient clinic for three years with arsphenamin, mercury, and potassium iodid   At the end of this time the patient was symptom-free and X-ray examination showed that the osteomyelitis of the skull had entirely healed.   The blood Wassermann test was negative, and the cerebrospinal fluid was entirely normal

Treatment and results   The individual patients in this group received various types of treatment.   All but 2 of the cases, however, were treated with intravenous injections of an arsenical drug and intramuscular injections of bismuth or mercury   Thirteen cases received Swift-Ellis intraspinous treatment and 4 cases were treated with intravenous injections of tryparsamide

Two cases did not receive any anti-luetic therapy   Case 63 refused treatment and was taken home against advice   He died at home two years later with a right hemiplegia and dementia   Case 67 had a decompression operation four days after admission to the hospital and died immediately after the operation as the result of post-operative sub-dural bleeding

With the exception of the above 2 cases, all the remaining cases were discharged from the hospital entirely relieved of the symptoms present on admission, or very much improved   In several instances the cranial nerve palsies improved very slowly and slight residuals of the palsies were present for several months after discharge.   In case 60, the third nerve palsy was permanent

Sixteen cases were followed for periods varying from two to fifteen years   Eleven cases were classed as clinical recoveries.   In 8 of these, the cerebrospinal fluid was entirely normal at the end of the period of observation and in the remaining 3 cases examination of the cerebrospinal fluid was not obtained   Two cases (nos 56 and 68), developed dementia paralytica.   One case (no. 48) showed persistent abnormalities in the cerebrospinal fluid of the "paretic" type four and a half years after the onset of the meningitis; the patient complained

of headache and showed Argyll Robertson pupils six years after the meningitis, but the cerebrospinal fluid was not examined at this time The ultimate outcome in this case is doubtful

Case 60 showed a progression of the cranial nerve palsies and had a first-zone gold curve when last examined three years after the meningitis

Case 75 was clinically recovered when examined two and a half years after the meningitis, but the cerebrospinal fluid still showed abnormalities

A brief abstract of these cases (with the exception of case 60, which has been previously given) is presented below

Case 48 D M, a 28-year old white male was admitted to the hospital March 11, 1926, complaining of headaches, vertigo, nausea, and vomiting of two weeks duration   He had a penile chancre ten weeks before entry and received eight intravenous injections, the first four weeks after the appearance of the chancre   He lapsed from treatment until three weeks before admission, when he received one intramuscular injection of mercury On admission patient showed blurring of the optic discs, paralysis of the left third, right fifth, seventh, and twelfth nerves, and stiffness of the neck The blood Wassermann reaction was positive   The cerebrospinal fluid was under increased pressure, it contained 740 lymphocytes per cubic millimeter, the globulin test was 2 plus, the colloidal gold reaction 1122100000, and the spinal fluid Wassermann reaction was positive   Patient remained in the hospital eighteen days during which time he received four intravenous injections of salvarsan (0 35 gram each) and two intraspinous (Swift-Ellis) treatments   He was discharged to return to the out-patient department for treatment   He attended very irregularly and received about eighteen injections of mercury between April and December, 1926   He lapsed from treatment and did not return until September, 1930, when his blood Wassermann was positive and the cerebrospinal fluid examination on December 3, 1930, showed 45 cells and positive Wassermann   The colloidal gold reaction was 4444442000   He received irregular treatment from September, 1930 to August, 1932, consisting of twelve injections of neosalvarsan, twelve injections of bismuth, and seven injections of tryparsamide   When last seen in August, 1932, patient was complaining of headaches, the pupillary reactions were of the Argyll Robertson type and the blood Wassermann was positive   Reexamination of the cerebrospinal fluid was not obtained

Case 56 H M , an 18-year old white male was admitted to the hospital November, 1914, with the complaints of headache, nausea, and vomiting of one month's duration   For the past two or three weeks his vision had become progressively worse and he had been seeing double   Patient had a chancre six months previously and a secondary rash four months before admission   He received three injections of salvarsan at the time of the appearance of the rash   On examination a fading secondary rash was visible   There was stiffness of the neck and bilateral Kernig's sign   The optic discs were choked and there was a marked impairment of visual acuity   The right third and sixth cranial nerves were paralyzed and the deep reflexes were increased   Lumbar puncture on admission showed the cerebrospinal fluid to be under increased pressure   It contained 550 cells, 90 per cent of which were mononuclears, and the Wassermann reaction was positive on 0 1 cc of fluid   The blood Wassermann reaction was negative The patient remained in the hospital for three weeks during which time he received three injections of salvarsan, two Swift-Ellis intraspinous treatment, mercury succinimide injections, and potassium iodid   He was discharged relieved of the symptoms present on entry   The choked discs had receded and the cranial nerve palsies had disappeared

Between December, 1914 and September, 1915, the patient received eighteen injections of salvarsan (0 4 gram each), twelve Swift-Ellis intraspinous treatments, and three intramuscular injections of mercury   He had three convulsive seizures in March, 1915   In July, 1915, the cerebrospinal fluid Wassermann was negative on 1 0 cc , and contained only 7 cells per cubic millimeter

From 1916 to 1919 the patient received irregular treatment in the outpatient department, chiefly mercury succinimide (thirty injections)   He was in the Army during the war, where he received intravenous treatment (amount unknown) and was said to have had a negative lumbar puncture His blood Wassermann reaction was negative in May, 1919, and February, 1920

The patient lapsed from observation until May, 1924   At this time his pupils were irregular but reacted normally   The deep tendon reflexes were hyperactive   The blood Wassermann reaction was positive   The cerebrospinal fluid contained 20 lymphocytes, the globulin reaction was positive, the colloidal gold reaction 4555542110, and the spinal fluid Wassermann reaction was positive in dilutions of 0 1 cc   After the lumbar puncture a transient paresis of the right arm and face set in   From June, 1924, to September, 1924, he received thirteen injections of arsenobenzol (0 4 gram each) and seven intraspinous treatments.   In September, 1924, the blood

Wassermann was positive, the cerebrospinal fluid contained 6 cells, the gold curve was 3332211000, and the Wassermann reaction was positive in 0 5 cc

The patient moved to New York and was not seen again until August, 1928, when he was brought to the clinic by his mother   She stated that he had had a series of convulsions in New York and that she had received a telegram from a New York hospital advising her of his admission to the hospital

On admission to the Boston Psychopathic Hospital in August, 1928, the patient was optimistic and euphoric   He was disoriented as to time, and his memory for recent and remote events was poor   He was unable to concentrate and his calculations were poor   He was orderly and well-behaved   There were no delusions, hallucinations or insight into his condition   The speech was slurring   Pupils were irregular and reacted poorly to light and the deep reflexes were hyperactive   The blood Wassermann was positive   The cerebrospinal fluid contained 140 cells, the globulin test was positive, total protein content was 105 mgm , the colloidal gold curve 5555554100, and the Wassermann was positive in 0 1 cc   The patient was inoculated with malarial organisms and had thirteen paroxysms of fever   He was discharged from the hospital as improved on October 18, 1928   From November, 1928 to February, 1929, he received ten injections of tryparsamide (3 0 grams each), and nine injections of arsphenamin (0 3 gram each)   Examination of the cerebrospinal fluid in February, 1929, showed 10 cells, total protein 68 mgm , colloidal gold 5555554321, and a positive Wassermann in 0 1 cc of fluid

The patient left the city in February, 1929 to return to New York   A letter was received from the patient in December, 1932, stating that he was in good health and working   We have been unable to obtain any information as to his present status

Case 68   R F , a 38-year old white male, admitted to the hospital January 10, 1922, with complaint of severe headaches and diplopia of two weeks duration   He gave a history of a primary sore sixteen years ago, but had no knowledge of a secondary rash   He had been receiving almost continuous treatment for the past two and a half years, which consisted of thirty injections of diarsenol and seventy-five injections of gray oil of mercury   His last treatment was an injection of gray oil seven weeks before entry   The examination on admission showed stiffness of the neck, irregular pupils, reacting poorly to light, paralysis of the left 3d and 6th cranial nerves, and hyperactive reflexes   The blood Wassermann was positive   The cerebrospinal fluid contained 1650 cells, 95 per cent lympho-

cytes, and the Wassermann reaction was positive   Patient remained in hospital one week and was discharged improved

He was treated continuously in the out-patient department from January, 1922, to April, 1926, receiving alternate courses of an arsenical drug (neosalvarsan, diarsenol, or tryparsamide) and intramuscular injections of bismuth, and also fourteen intraspinous treatments   The blood Wassermann remained positive   The cerebrospinal fluid on repeated examination consistently showed a mild pleocytosis (10 to 15 cells), increased protein, a strong gold curve (5555554321), and a strongly positive spinal fluid Wassermann reaction   The patient lapsed from treatment in June, 1926, and became psychotic in August, 1927   He was admitted to the Boston Psychopathic Hospital, where he was found to be confused, talkative, and to show marked mental deterioration   The speech was slurring   Pupils were irregular but reacted to light, and the deep reflexes were hyperactive. The cerebrospinal fluid showed 44 lymphocytes, a markedly positive globulin reaction, a colloidal gold curve of 5555331000   The blood and cerebrospinal fluid Wassermann reaction were strongly positive   He was committed to the Boston State Hospital in August, 1927, where he was still living in February, 1934   He was inoculated with malaria and was given many injections of tryparsamide, but has continued to go down-hill mentally and at present is so deteriorated that it is not possible to gain contact with him

Case 75   M Z , a 30-year old white male was admitted to the hospital August 18, 1920, with complaints of pain and stiffness in the neck   There was no history of a primary sore, secondary rash, or any previous antiluetic therapy   On examination, he showed stiffness of the neck and paralysis of the left third and seventh nerves   The blood Wassermann reaction was negative   The cerebrospinal fluid contained 145 lymphocytes, and the Wassermann reaction was positive on 0 2 cc of the fluid   He was treated continuously for the next two and a half years with intramuscular injections of mercury, intravenous injections of diarsenol, and seven intraspinous treatments   The blood Wassermann became positive but was negative in January, 1923.   Lumbar puncture on January 28, 1923, showed 3 cells per cubic millimeter, a positive globulin test, and a positive Wassermann reaction on 1 0 cc of the spinal fluid

III ANALYSIS OF SEROLOGICAL FINDINGS

Since the serological findings were very similar in all three groups of cases, it was thought advisable to analyze them together   In

tables 1, 2, and 3, the blood Wassermann reaction and the findings in the cerebrospinal fluid at first puncture are given

The blood Wassermann reaction   Table 4 shows the results of the blood Wassermann test in the 74 cases in which it was recorded, divided into two groups according to the time after the initial infection that the meningitis developed   The blood Wassermann test was positive in 48 cases (64 per cent) and negative in 26 cases (36 per cent)   Thus, *more than one-third of the total number of cases had a negative blood Wassermann test   This fact indicates the unreliability of the blood serological tests in excluding syphilis of the central nervous system   This fact is even more strongly shown in the 20 cases in which there was no history of a primary infection   Exactly 50 per cent of these cases had a*

TABLE 4

Analysis of the blood Wassermann reaction in 80 cases of acute syphilitic meningitis, arranged according to the time after infection that the meningitis occurred

BLOOD WASSERMANN REACTION	TIME AFTER APPEARANCE OF PRIMARY LESION			
	Less than 2 years	More than 2 years	Unknown	Totals
Positive	25	13	10	48
Negative	13	3	10	26
Not recorded	4	1	1	6
	42	17	21	80

negative blood Wassermann test   The highest percentage of positive blood Wassermann reactions occurred in the cases in which the meningitis developed more than two years after the initial infection   In 13 of these 16 cases, the reaction was positive (81 per cent)

The cerebrospinal fluid   The cerebrospinal fluid was examined in every case and the findings at first puncture are presented in tables 1, 2, and 3

Pressure   The cerebrospinal fluid pressure was measured in 47 cases   The results varied from 80 to 520 (millimeters of cerebrospinal fluid) with an average of 260 mm   In 16 cases, or 34 per cent of these 47 cases, the pressure was under 200 mm of spinal fluid   In the remaining 31 (66 per cent) the pressure was above 200 mm and in 7 cases (15 per cent) the pressure was above 400 mm of cerebrospinal fluid

Appearance of fluids   In most cases the fluid was clear and color-less   The fluids which contained a large number of cells were ground-glass or turbid in appearance   Several of the fluids were xanthochro-mic   A delicate fibrin clot formed in most of the fluids if they were allowed to stand over-night

Cell count   The cell count was done in all cases, and it varied from 2 to 2000, with an average of 434 (table 5)   The cell count was under 100 in 20 cases (25 per cent), and was between 100 and 1000 in 52 cases (65 per cent)   The cell count was over 1000 in 8 cases, (10 per cent)   There were less than ten cells in only 1 case   In a major-ity of cases the cells were almost wholly of the lymphocytic or mono-nuclear series   In 55 cases the percentage of polymorphonuclear leu-

TABLE 5

Analysis of the number of white blood cells found in the cerebrospinal fluid of 80 cases of acute syphilitic meningitis

CELLS PER CUBIC MILLIMETER	NUMBER OF CASES	PER CENT
Less than 10	1	1
11– 50	14	18
51– 100	5	6
101– 500	28	35
501–1,000	24	30
1,000–2,000	8	10
	80	100

High, 2,000   Low, 2   Average, 434

kocytes were given and varied from 0 to 80 per cent, with an average of 12 per cent   In 3 cases there was more than 50 per cent polymor-phonuclear leucocytes in the spinal fluid

Globulin test   These tests were done in 76 cases   They were nega-tive in 9 cases, positive in 32 cases, and markedly positive in 35 cases

Protein   The protein content was determined in 52 cases (table 6). The results varied from 23 to 381 mgm per 100 cc , with an average of 110   The protein content was within normal limits (under 45 mgm per cubic centimeter) in 6 cases   In 4 of these cases the globu-lin test was negative and in the other 2 cases the globulin reaction was not recorded   In 40 per cent of the cases the total protein was be-tween 45 and 100 mgm and in 38 per cent of the cases it was between 100 and 200 mgm

Sugar The sugar content of the fluids was measured in 31 cases They ranged between 18 and 84, with an average of 49 mgm per 100 cc Table 7 shows the range of figures In 17 cases (55 per cent) the sugar content was less than 50 mgm per 100 cc

A decrease in the sugar content in these cases has been previously noted by Mestrezat (1912) and other observers The cause of the

TABLE 6

Analysis of the protein content in the cerebrospinal fluids obtained at first puncture of 52 cases of acute syphilitic meningitis

PROTEIN CONTENT	NUMBER OF CASES	PER CENT
mgm per 100 cc		
Less than 45 (normal)	6	12
46–100	21	40
101–200	20	38
201–381	5	10
	52	100

High, 381   Low, 23   Average, 110

TABLE 7

Analysis of the sugar content in the cerebrospinal fluids obtained at first puncture in 31 cases of acute syphilitic meningitis

SUGAR CONTENT	NUMBER OF CASES	PER CENT
mgm per 100 cc		
Less than 30	3	10
31–40	11	35
41–50	3	10
51–75	10	32
76–84	4	13
	31	100

High, 84   Low, 18   Average, 49

low sugar content is not definitely known, but it is thought to be due to the glycolytic action of the spirochetes present in the meninges and in the spinal fluid

Chloride The chloride content was determined in 23 cases (table 8) It varied from 636 to 742 mgm per 100 cc , with an average of 695 In 3 cases the chloride content of the fluid was between 636 and 650 and in 8 cases it was between 650 and 700 The reduction

Appearance of fluids　In most cases the fluid was clear and color-
less　The fluids which contained a large number of cells were ground-
glass or turbid in appearance　Several of the fluids were xanthochro-
mic　A delicate fibrin clot formed in most of the fluids if they were
allowed to stand over-night

Cell count　The cell count was done in all cases, and it varied from
2 to 2000, with an average of 434 (table 5)　The cell count was under
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per cent)　There were less than ten cells in only 1 case　In a major-
ity of cases the cells were almost wholly of the lymphocytic or mono-
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TABLE 5

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CELLS PER CUBIC MILLIMETER	NUMBER OF CASES	PER CENT
Less than 10	1	1
11– 50	14	18
51– 100	5	6
101– 500	28	35
501–1,000	24	30
1,000–2,000	8	10
	80	100

High, 2,000　Low, 2　Average, 434

kocytes were given and varied from 0 to 80 per cent, with an average
of 12 per cent　In 3 cases there was more than 50 per cent polymor-
phonuclear leucocytes in the spinal fluid

Globulin test　These tests were done in 76 cases　They were nega-
tive in 9 cases, positive in 32 cases, and markedly positive in 35 cases

Protein　The protein content was determined in 52 cases (table 6)
The results varied from 23 to 381 mgm per 100 cc, with an average
of 110　The protein content was within normal limits (under 45
mgm per cubic centimeter) in 6 cases　In 4 of these cases the globu-
lin test was negative and in the other 2 cases the globulin reaction was
not recorded　In 40 per cent of the cases the total protein was be-
tween 45 and 100 mgm and in 38 per cent of the cases it was between
100 and 200 mgm

Sugar   The sugar content of the fluids was measured in 31 cases
They ranged between 18 and 84, with an average of 49 mgm per 100
cc   Table 7 shows the range of figures   In 17 cases (55 per cent) the
sugar content was less than 50 mgm per 100 cc

A decrease in the sugar content in these cases has been previously
noted by Mestrezat (1912) and other observers   The cause of the

TABLE 6

*Analysis of the protein content in the cerebrospinal fluids obtained at first puncture of 52 cases
of acute syphilitic meningitis*

PROTEIN CONTENT	NUMBER OF CASES	PER CENT
mgm. per 100 cc		
Less than 45 (normal)	6	12
46–100	21	40
101–200	20	38
201–381	5	10
	52	100

High, 381   Low, 23   Average, 110

TABLE 7

*Analysis of the sugar content in the cerebrospinal fluids obtained at first puncture in 31 cases
of acute syphilitic meningitis*

SUGAR CONTENT	NUMBER OF CASES	PER CENT
mgm per 100 cc		
Less than 30	3	10
31–40	11	35
41–50	3	10
51–75	10	32
76–84	4	13
	31	100

High, 84   Low, 18   Average, 49

low sugar content is not definitely known, but it is thought to be due
to the glycolytic action of the spirochetes present in the meninges and
in the spinal fluid

Chloride   The chloride content was determined in 23 cases (table
8)   It varied from 636 to 742 mgm per 100 cc , with an average of
695   In 3 cases the chloride content of the fluid was between 636
and 650 and in 8 cases it was between 650 and 700   The reduction

in the cerebrospinal fluid chlorides is due to a fall in the serum chlorides associated with fever

Colloidal gold This test was performed in 56 cases (table 9) A first zone (paretic curve) occurred in 22 cases, a mid-zone (luetic) curve in 28 cases, and an end-zone (meningitic) curve in 3 cases *In only 3 cases was there a normal colloidal gold test* Twenty-two cases had a first-zone (paretic) gold curve at first puncture Nine of these cases

TABLE 8

Analysis of the chloride content in the cerebrospinal fluids obtained at first puncture in 23 cases of acute syphilitic meningitis

CHLORIDE CONTENT (AS NaCl)	NUMBER OF CASES	PER CENT
mgm per 100 cc		
636–650	3	13
651–700	8	35
701–742	12	52
	23	100

High, 742   Low, 636   Average, 695

TABLE 9

Analysis of the colloidal gold reaction in the cerebrospinal fluids at first puncture in 56 cases of acute syphilitic meningitis

TYPE OF COLLOIDAL GOLD CURVE	NUMBER OF CASES	PER CENT
First zone (paretic)	22	40
Mid-zone (luetic)	28	50
End-zone (meningitic)	3	5
Normal	3	5
	56	100

had an examination of the cerebrospinal fluid two or more years later. In 7 of these cases the patients were clinically recovered and the cerebrospinal fluid was entirely normal One case (no 14) was clinically recovered and the cerebrospinal fluid was normal except for a colloidal gold curve of the mid-zone type (123332100) In 1 case (no 68) there developed clinical signs of dementia paralytica and the cerebrospinal fluid remained abnormal with a first-zone gold curve These facts are presented to show that the first-zone colloidal gold curve has no prognostic significance in these cases

Cerebrospinal fluid Wassermann   The Wassermann test was performed on the cerebrospinal fluid of every case (table 10)   The test was positive in 69 cases (86 per cent), and negative in 11 cases (14 per cent) All of the cases with negative cerebrospinal fluid Wassermann reactions showed abnormalities in the fluid indicating an active meningitis, that is, pleocytosis, increased protein or abnormal gold curve   In 4 of these 11 cases, the Wassermann test was positive in one or more of the fluids obtained at subsequent punctures   It is interesting to note that 8 of the 11 cases with negative cerebrospinal fluid Wassermann reactions were women

IV REPORT OF A FATAL CASE WITH PATHOLOGICAL FINDINGS

Case 67 C H , white male, aged 38, was admitted to the hospital November 18, 1922, with complaint of progressive loss of vision for past four weeks and headaches of moderate degree for the same period   He

TABLE 10

Analysis of the cerebrospinal fluid Wassermann on first puncture of 80 cases of acute syphilitic meningitis

WASSERMANN REACTION		NUMBER OF CASES	PER CENT
Positive		69	86
Negative		11	14
Total		80	100

gave a history of primary sore 15 years previously   There was no history of secondary rash or anti-luetic treatment   The examination on admission showed unequal pupils which reacted sluggishly   The visual acuity was restricted to light perception in the temporal fields   Examination of the fundi showed 4 diopter of swelling of the discs   The remainder of the examination was negative   The blood Wassermann reaction was positive The cerebrospinal fluid was under a pressure of 520 mm of cerebrospinal fluid   The fluid was clear and colorless and contained 146 cells per cubic millimeter   The protein content was 133 mgm and the sugar content was 40 mgm per 100 cc   The colloidal gold reaction was 1455555321 and the cerebrospinal fluid Wassermann was strongly positive

On account of the high cerebrospinal fluid pressure and marked loss of vision a subtemporal decompression was performed November 22, 1922 The following morning the patient had a convulsive seizure and died

The necropsy on November 23, 1922, showed syphilitic aortitis, syphilitic orchitis, oedema of the lungs and hemorrhage beneath the dura at the site of the operative wound   The pia over the surface of the brain appeared somewhat cloudy   The optic nerves were grossly normal   Microscopic examination of the meninges showed an infiltration with mononuclear cells, chiefly of the lymphocytic type with no special localization of the inflammation around the vessels   Stains for spirochaetes were negative   Examination of the optic nerves showed moderate infiltration of the pia-arachnoid especially in the neighborhood of the chiasm   There was a marked neuroglial proliferation in the optic nerve and proliferation of, the fixed cells of the meninges around the nerve   Spirochaete stains of- the optic nerve were negative.

V DISCUSSION

Frequency   Our series of cases offers no actual statistics as to the frequency of acute syphilitic meningitis   We were able to find only 80 well-authenticated cases in the past fifteen years in three general hospitals with a total bed capacity of over two thousand, which would indicate that it is a relatively rare occurrence   The literature on the subject is conflicting   Finger (1911) found 44 cases in 500 early syphilitics   He claimed that 9 per cent was the approximate incidence of this complication and criticized Benario's (1911) much lower figure on the ground that the latter's statistics were based on results in clinics where many "floaters" were treated and many cases were not followed   The most valuable statistics on this subject are those from Moore's clinic at the Johns Hopkins Hospital   Zimmerman (1922) found 23 cases in 1400 cases of early syphilis, or an incidence of 1 6 per cent   Moore in 1929 reported 55 neurorecurrences in 2675 cases of primary or secondary syphilis, or an incidence of 0 2 per cent   Stokes states that these cases are comparative rarities even in a special practice   If the figures of Moore and Zimmerman (0 2 and 1 6 per cent) are accepted as representing the frequency in early syphilis, the total incidence would be about 50 per cent greater, or 0 3 to 2 4 per cent, since our findings indicate that about two-thirds of the cases occur as a complication of early syphilis

Sex incidence   Eighty cases showed the following distribution as to sex· male, 48, and female, 32   This relationship is not greatly different from the incidence of primary syphilis in the two sexes as given by

Finger[1] (1175 men to 842 women) It is in marked contrast, however, to the figures of Moore (1929) (72 males, 17 females) Rothschild's (1927) figures are more in accord with ours 31 males, 17 females Mattauschek's series is the only one in which there was a preponderance of females (2 males, 7 females) His series is too small to be of any statistical value Our series, and to a lesser degree that of Rothschild, would indicate that females suffer from syphilitic meningitis only a little less frequently than males This is of considerable immunological significance when compared to the frequency of parenchymatous neurosyphilis in the two sexes where the relationship is approximately as 5 cases in the male to 2 in the female This differ-

TABLE 11

The age incidence of acute syphilitic meningitis

AGES	NUMBER OF CASES	PER CENT
years		
Under 19*	7	9
20–29	33	41
30–39	27	34
40–49	8	10
50–56	5	6
	80	100

* Includes 2 cases of congenital syphilis

ence in the incidence of parenchymatous neurosyphilis in the two sexes indicates that the female develops an immunity to this type of neurosyphilis Moore (1922) attributes this difference of incidence of parenchymatous neurosyphilis in the two sexes as being due to the protective action of pregnancy in the female Our statistics as to the slight inequality of the incidence of syphilitic meningitis in the two sexes does not disprove this hypothesis, since syphilitic meningitis is essentially a complication of early syphilis, before any protective effect of pregnancies could be manifested

Age incidence The age incidence in our cases varied from twelve to fifty-six (table 11) The great majority of the cases (75 per cent) occurred between the ages of nineteen and thirty-nine Our statistics

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Age incidence   The age incidence in our cases varied from twelve to fifty-six (table 11)   The great majority of the cases (75 per cent) occurred between the ages of nineteen and thirty-nine   Our statistics

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are in agreement with those of Rothschild (1927) and show that acute syphilitic meningitis may occur at any age   Two of our cases occurred in congenital syphilitics   Such cases have been previously reported by Bly (1918), Leitch (1918), Babonneix (1928), and Mikulowski (1932)   It is also a frequent observation that congenital syphilitics may show marked serological evidence of meningeal involvement without clinical signs of such involvement   There were no cases in our series older than sixty years and we have not found any such cases in the literature   This is accounted for in part by the fact that primary syphilis is rare after the age of sixty

Racial incidence   Acute syphilitic meningitis has been reported in all races   Several of our cases were negroes, and there was one

TABLE 12

Length of time between the primary infection and the occurrence of the meningitis in the 59 cases in which this interval could be determined

TIME AFTER THE PRIMARY LESION	ACUTE SYPHILITIC HYDROCEPHALUS	VERTICAL MENINGITIS	BASILAR MENINGITIS	TOTAL	PER CENT
years					
Less than 1	16	9	13	38	64
1–2	1	2	1	4	7
2–6	1	1	4	6	10
Over 6	1	3	7	11	19
	19	15	25	59	100

Chinaman, several Italians, one German, and one Greek in our series The majority of the patients in the Boston clinics are American-born whites, so our statistics are of no value in this regard   Moore's (1929) statistics are of value in regard to the incidence of syphilitic meningitis in the negro race   In his clinic, neurorecurrences were approximately twice as frequent in the white race as in the negro race

Length of time after primary infection at which the meningitis developed   Table 12 shows that while the meningitis may occur at any time after the infection, it usually occurs within one year of the initial infection   This is true regardless of the type of the meningitis, although a much higher percentage of the basilar cases occurred six or more years after the infection than either of the other two types   The statistics in the literature in this regard are difficult to evaluate since

most of the cases reported are of the neurorecidive type which, by definition, must occur early   There are, however, numerous examples in the literature showing that the meningitis may occur at any stage, and may be a complication of any form of neurosyphilis   Its occurrence in congenital syphilis has been previously noted   It may occur in the so-called latent period as shown in our cases, Friedman's cases (1926), and by the cases of Gennerich (1922) and Nonne (1924) Nonne (1924) cites several cases in which the meningitis was a complication of tabes dorsalis or dementia paralytica and in our series 2 cases occurred as a complication of tabes dorsalis (one congenital and one acquired) and in 1 case (no 68) the meningitis was possibly a complication of early dementia paralytica

TABLE 13

Relative frequency of a history of the occurrence of the early lesions of syphilis in 80 cases of acute syphilitic meningitis

	ACUTE SYPHILITIC HYDRO CEPHALUS	VERTICAL MENINGITIS	BASILAR MENINGITIS	TOTAL	PER CENT
Chancre	13	11	21	45	56
Secondary rash	12	9	11	32	40
Both	7	5	8	20	25
Neither	8	5	10	23	29

In our series there were 21 (26 per cent) in which there was no history of a primary sore or a secondary rash   Gennerich emphasized the frequency of meningitis in these so-called "luesignorée" cases and stated that the danger of meningitis is especially great in the disease Table 13 shows the frequency of a history of the occurrence of primary and secondary manifestations in our cases   A history of a primary lesion was given in 45 cases (56 per cent), and of a secondary rash by 32 cases (40 per cent)   This is of interest in comparison to the much smaller percentage of cases of parenchymatous neurosyphilis, with a history of secondary manifestations   *A secondary rash was present in 6 cases at the time of their admission to the hospital with the meningitis*

Influence of previous therapy on the onset of the meningitis   In 29 of our cases (36 per cent) there was no history of any previous antiluetic therapy   In all of the remaining cases the meningitis developed during a lapse in therapy with the exception of 3 cases in which the

symptoms developed while receiving intramuscular injections of mercury.

In the cases in which the meningitis developed during a lapse from treatment, the interval between the last treatment and the onset of symptoms varied from three weeks to several years   In most cases the interval was from four to eight weeks   Table 14 shows the type of treatment these patients had received before the lapse in treatment Twenty cases had received intravenous injections of one of the arsenical drugs, 20 cases had received an intravenous arsenical drug and intramuscular injections of mercury, 9 cases an intravenous arsenical drug and intramuscular injections of bismuth and 2 cases had received only intramuscular bismuth   *The meningitis developed in 31 of our cases (39 per cent) who had not received any of the arsphenamines*   The

TABLE 14

Type of therapy prior to the onset of the meningitis

TYPE OF THERAPY	NUMBER OF CASES	PER CENT
Intravenous arsenicals—alone	20	25
Intravenous arsenicals plus intramuscular mercury	20	25
Intravenous arsenicals plus intramuscular bismuth	9	11
Intramuscular bismuth—alone	2	3
No anti-luetic therapy	29	36
	80	100

development of meningitis in untreated patients has been reported in practically every study on the subject   The immunological significance of these cases will be discussed later

The meningeal symptoms did not develop in any of our cases during active arsenical or bismuth therapy, but the onset of the meningitis occurred in 3 of our cases while the patients were receiving intramuscular injections of mercury   Four of Moore's cases developed while the patients were taking mercurial inunctions   Syphilitic meningitis may occur after a lapse in bismuth therapy as shown by nine cases in our series as well as by the cases of Nathan (1925), Rothschild (1927), Moore (1929), and Solomon (1932)   Nathan claims that the interval between the date of the lapse from treatment and the onset of the meningitis is prolonged in the cases that have received bismuth in-

jections   He attributes this to the slowness of excretion of bismuth
In our 9 cases the interval between the last bismuth injection and the
onset of symptoms of meningitis varied from five weeks to two months
in all of the cases except 2   These 2 cases had received bismuth in-
jections several years before the onset of the meningitis

Moore (1929) emphasizes the importance of a large dosage of salvar-
san in the treatment of early syphilis in the prevention of syphilitic
meningitis   He recommends the injection of 0 1 gram salvarsan per
25 pounds of body weight for the first three treatments   His figures
in support of this contention are not especially convincing since his
frequency of incidence in 1926 and 1927 was not greatly different from
that in 1918, when such dosage was not used   There is, however, con-
siderable merit to his contention for more arsenical treatment of early
syphilis as shown by the fact that only 8 of our cases had received more
than ten injections of an arsenical drug before the onset of the men-
ingitis

The case reported by Solomon (1932) shows that the meningeal
symptoms can develop after active bismuth and arsenical therapy,
and after a lumbar puncture had shown a normal cerebrospinal fluid
In his case, a negative blood Wassermann and normal cerebrospinal
fluid findings were obtained in a case six months after the primary
infection, during which time the patient had received fifteen injections
of neoarsphenamin and nine injections of bismuth   The patient be-
gan to complain of very severe headache which persisted in spite of
seven injections of bismuth, two injections of neoarsphenamin, and
eight injections of silver-arsephenamin   In view of the previously
negative cerebrospinal fluid, the diagnosis of syphilitic meningitis was
thought improbable but a lumbar puncture fourteen months after in-
fection showed 204 cells, a total protein of 150 mgm per 100 cc and a
colloidal gold curve of 4555555554   The blood Wassermann was posi-
tive, but the cerebrospinal fluid Wassermann was negative   The
patient was clinically cured by intensive tryparsamide therapy

It is obvious, therefore, that syphilitic meningitis can occur while
the patient is receiving standard, or so-called "adequate" therapy,
*but we have not seen or found in the literature reports of any case that
developed during active arsenical therapy   The development of meningeal
symptoms indicates that the treatment the patient is receiving is inade-*

*quate for him and that arsenical treatment should be more vigorously
pursued*

The prevention of acute syphilitic meningitis is a difficult problem
and depends to a large extent on the efficient treatment of early syphi-
lis since it is usually a complication of this stage   Several facts are
important   (1) syphilitic meningitis is uncommon if the patient re-
ceives a long course of one of the arsphenamins (fifteen to thirty injec-
tions) as the initial treatment, and (2) it is rare unless the patient
lapses from treatment within the first year after the injection   There-
fore the patient should receive continuous treatment for at least the
first year   Intramuscular injections of bismuth should be used in-
stead of mercurial inunctions or rest periods   *Diligent follow-up work
is necessary to prevent lapses in treatment*

Clinical syndrome   The cases of acute syphilitic meningitis may be
divided into three groups in accordance with the appearance of symp-
toms and signs indicating localized involvement of the meninges

In the first group, the symptoms are those of a rapidly developing
hydrocephalus without cranial nerve palsies, convulsions, or focal
signs   These cases differ only in degree from the much more
frequent cases of secondary syphilis with mild or moderately
severe headache and cerebrospinal fluid change indicating meningeal
involvement   The severity of the headaches, associated with nausea
and vomiting, stiffness of the neck, and choked discs, indicate that the
meningeal involvement is especially severe and justify the establish-
ment of these cases as a clinical entity   It is probable that the symp-
toms in these cases are due to an interference in the circulation of the
cerebrospinal fluid by the inflammation in the posterior fossa around
the basal cisterns, producing an internal hydrocephalus   We have,
therefore, called this group acute syphilitic hydrocephalus   The divi-
sion of the remaining cases into vertical and basilar types has been in
use for many years, and was especially popularized by Nonne and by
Gennerich   The purpose of this division is to emphasize the fact that
the site of the most marked involvement of the meninges varies in the
different types   This division is chiefly a clinical one since most of
the autopsied cases have shown a rather wide-spread meningeal in-
volvement   In some cases, however, the meninges at the base have
shown greater involvement than those of the vertex, and *vice versa*

It has also been already demonstrated that the cases do not always fall wholly within one of the three types since signs of acute hydrocephalus are present in many of the cases of the basilar and vertical types, and cranial nerve palsies may occur in cases with convulsions and mental signs

This combination has also been previously noted by Nonne and Rothschild, but the striking fact is the rarity of its occurrence We found the combination of basilar and vertical signs and symptoms in only 2 of our 80 cases, and Gennerich (1922) and Moore (1929) did not find any examples in their series

Symptomatology Headache, nausea, and vomiting These are the most common symptoms They were present in 73 of our 80 cases (91 per cent) The cause of these symptoms is not definitely known They are not directly related to the level of the intracranial pressure, but the cerebrospinal fluid pressure was elevated in practically all the cases that had these symptoms Nonne (1924) suggests that the headache is possibly due to involvement of the dura mater He bases his statement on the fact that the dura is the only covering of the brain that has pain fibres, and also that the skull in some of the cases showed localized areas of tenderness to percussion The occurrence and nature of these symptoms in acute syphilitic meningitis is no different than in tumors of the brain, and it is probable, therefore, that the mechanism of these symptoms is the same in the two, i e , increased intracranial pressure

Mental symptoms Mental symptoms were present in 12 of our cases (15 per cent) and they have been reported by most other observers They are explained as due to involvement of the meninges over the vertex of the hemispheres, especially over the frontal lobes

Convulsions Convulsive phenomena were present in 14 of our cases (17 per cent) These convulsive phenomena were either in the nature of generalized convulsions or *petit mal* attacks Jacksonian attacks, although they did not occur in our series, have been observed by other authors (Nonne, 1924) It is noteworthy that one of the cases (no 31) continued to have convulsions for the eleven years that she was observed, although she was otherwise symptom-free and the cerebrospinal fluid was entirely normal This was probably due to a meningeal scar This observation may be of importance in relation-

ship to the occurrence of convulsions in congenital syphilitics with normal cerebrospinal findings

Focal lesions Focal symptoms and signs were present in 4 of our cases (5 per cent). In 3 cases there was a hemiplegia and 1 case showed transient attacks of aphasia These focal signs have been reported by most other observers and are explained on the basis of a thrombosis of, or a functional disturbance of the circulation in, one of the cortical or sub-cortical arteries as a result of syphilitic arteritis Focal signs, when they occur, are usually confined to the sensorimotor and speech centers Involvement of the central visual areas is relatively rare

Fever Fever was not a prominent symptom in our cases A slight elevation in the temperature was present in most of the cases the first week after admission Temperature readings over 101°F were very rare Margulis (1926) and Pette (1921) have emphasized the occurrence of fever in these cases and the importance of considering syphilis as an etiology in meningitis with low-grade fever

Stiffness of the neck and Kernig's sign These were present in 47 of our cases (59 per cent) It was much more frequent in the acute hydrocephalus and vertical groups than in the basilar group. This would indicate that rigidity of the neck is related to involvement of the meninges over the vertex, or posterior fossa, rather than the meninges at the base of the brain

Pupillary reactions With the exception of the cases showing involvement of the third nerve, and in cases which occurred several years after the primary infection, the pupillary reactions to light and on accommodation were normal This is in agreement with the conception that the abnormalities in the pupillary reactions in neurosyphilis are of slow evolution

Three of the cases showed pupillary reaction of the Argyll Robertson type In these cases the meningitis developed six years, sixteen, and twenty years after the initial infection Two cases developed Argyll Robertson pupils while under observation six and fourteen years after the acute meningitis Thus, 5 cases were observed with pupillary reactions of the Argyll Robertson type The final results in these cases are interesting in regard to the controversy as to whether the Argyll Robertson pupil is due to a meningeal or parenchymatous

lesion   Two cases developed dementia paralytica, one case tabes dorsalis, one case recovered, and in one case the final results were not definitely known   At the end of six years observation, the patient still complained of headaches, and his cerebrospinal fluid remained markedly abnormal   Thus 3 (and probably 4) of the 5 cases who had Argyll Robertson pupils at the time of the meningitis, or in whom the condition developed later, subsequently exhibited evidence of parenchymatous neurosyphilis   We feel that this supports the contention that the lesion causing the Argyll Robertson pupil is central and parenchymatous in nature (Merritt and Moore, 1933)

TABLE 15

The relative frequency of involvement of the separate cranial nerves in 36 cases of acute syphilitic meningitis with cranial nerve palsies

CRANIAL NERVE	BILATERAL INVOLVEMENT	UNILATERAL INVOLVEMENT		TOTAL
		Right	Left	
II	6	0	0	6
III	0	6	6	12
IV	0	1	0	1
V	1	3	4	8
VI	2	3	4	9
VII	2	8	8	18
VIII	4	6	4	14
IX, X	1	2	2	5
XII	0	2	1	3
Total	16	31	29	76

Choked disc   Choked discs were present in 40 of the 69 cases (59 per cent) in which the examination of the fundi was recorded   In most instances it was directly related to the increased cerebrospinal fluid pressure, but it occurred in some cases with normal cerebrospinal fluid pressure   In such cases the swelling of the disc was probably due to an interference of lymphatic and venous drainage of the optic nerve by the meningitis or by an active neuro-retinitis

Cranial nerve involvement   Signs of involvement of one or more cranial nerves were present in 36 of our cases (45 per cent)   Table 15 shows the relative frequency with which the various cranial nerves were involved in our series   The cranial nerve involvement was con-

fined to one side of the brain-stem in 20 cases   A single nerve was involved in 6 cases, one pair in 5 cases, two different nerves in 11 cases, three nerves in 9 cases, and more than three nerves in 5 cases

Table 16 shows the relative frequency of the involvement of the separate cranial nerves in 195 cases with cranial nerve palsies compiled from the literature   Our cases are included in this series   This table shows that the seventh nerve (80 cases) and eighth nerve (82 cases) are most frequently involved, and that they are involved with

TABLE 16

Cranial nerve involvement in acute syphilitic meningitis

Compilation of data in the literature showing the relative frequency of involvement of the various cranial nerves in 195 cases of acute syphilitic meningitis with cranial nerve palsies

CRANIAL NERVE NUMBER	SERIES OF (A) CARR, (B) DOLIN, (C) GLASS, (D) SMITH	SERIES OF J E MOORE	SERIES OF GENNE- RICH	SERIES OF NONNE	SERIES OF ROTHS- CHILD	AUTHORS' SERIES	TOTALS
I	0	1	0	2	0	0	3
II	1	19	2	12	12	6	52
III	6	7	1	15	6	12	47
IV	1	1	0	2	0	1	5
V	4	0	0	11	0	8	23
VI	8	4	2	16	3	9	42
VII	5	23	7	16	11	18	80
VIII	4	31	9	11	13	14	82
IX, X	0	2	2	3	0	5	12
XI	1	0	0	0	0	0	1
XII	3	0	0	1	0	3	7
No of cases	15	63	16	41	24	36	195

approximately the same frequency   The second and third nerves were next most frequently involved, 52 and 47 cases respectively, followed in order by the sixth nerve (42 cases), fifth nerve (23 cases), ninth and tenth nerve (12 cases), twelfth nerve (7 cases), fourth nerve (5 cases), first nerve (3 cases), and eleventh nerve (1 case)

Involvement of the cranial nerves is confined to one side in approximately 60 per cent of the cases   The nerves involved have a tendency to fall into three groups (1) the interpeduncular, second and third nerves, (2) the cerebello-pontine angle, sixth, seventh, and eighth nerves, and (3) the bulbar group, tenth, eleventh, and twelfth nerves

This is not always true as the nerves may show involvement in a haphazard manner   In comparing the acute syphilitic meningitis with the chronic form of luetic meningeal reaction, Gennerich (1922) called attention to the fact that the early acute form had a predilection for the cerebello-pontine angle group of nerves, whereas the late and chronic forms tended to involve the nerves in the interpeduncular space   It is of interest to note that none of our cases showed polyuria or polydypsia, symptoms of involvement of the hypophyseal third ventricle region, which, according to Hirschl,[2] Gennerich (1922), and Nonne (1924), are not uncommon in the late chronic cases

The cranial nerve palsies in acute syphilitic meningitis are, as a rule, due to a disturbance of function of the nerve by the meningeal inflammation and in most cases the symptoms of the paralysis disappear with the subsidence of the inflammation   This is not always true, as shown by two of our cases in which the third nerve palsy persisted, and by the many cases in the literature in which unilateral or bilateral deafness persisted   Nonne (1924) stated that he has never seen an eighth nerve paralysis entirely disappear   We have also recently seen a case not included in this series with a permanent hemiatrophy of the tongue as a result of a twelfth nerve palsy in acute syphilitic meningitis   This case also showed bilateral weakness of the facial muscles and lacrimation on eating (the "crocodile tear" syndrome of Ford)   The persistence of the paralysis is explained usually on one of two bases   There is either a fibrosis of the meninges around the nerve causing a constriction of the nerve, or there has been a thrombosis of the nutrient artery of the nerve   The latter explanation is most plausible in the cases of persistent eighth nerve deafness of sudden onset

A special study of the incidence of the optic nerve involvement in syphilitic meningitis has been made by Drake (1933) and Uhthoff (1911), of facial nerve involvement by Strauss (1929), and of eighth nerve involvement by Mayer (1911), Lloyd (1921), and Nonne (1924)

Reflexes   Acute syphilitic meningitis has very little effect on the deep reflexes and no effect on the superficial reflexes unless there is evidence of a focal lesion   The deep reflexes were lively or increased in about 30 per cent of our cases, indicating possible irritation of the

the positive Wassermann reaction in the cerebrospinal fluid in such instances may well be due to the transference of syphilitic reagin from the blood serum to the cerebrospinal fluid (Jahnel, 1915)   The globulin test is practically always positive (a normal reaction was found in only 5 per cent of our 80 cases)   The colloidal gold curve may be of any type but the most common forms are the mid-zone (luetic), and first-zone (paretic) curves, 50 and 40 per cent respectively in our series

The cerebrospinal fluid Wassermann reaction is positive in a very high percentage of the cases, 89 per cent of our cases had a positive Wassermann reaction in the cerebrospinal fluid   It may be positive in 0 1 cc , but it is often negative in dilutions of less than 0 5 cc

The sugar content of the fluid is usually slightly reduced   This is thought to be due to the glycolytic action of the spirochetes present in the meninges   The sugar content, however, may be normal   This was true in 45 per cent of our cases   The chloride content of the fluid may be normal or slightly reduced, but the marked reduction that is found in the fluid from cases of tuberculous meningitis does not occur   The reduction in the cerebrospinal fluid chloride is due to reduction of the blood chloride, which is a common occurrence in any infection

Entirely normal spinal fluids have been reported in these cases, but they are extremely rare and throw the diagnosis into doubt   In our series there were no cases that had an entirely normal spinal fluid although several of our cases showed only one or two abnormalities in the fluid   This is also true of Rothschild's series   Six of the cases in Moore's series that had a normal cerebrospinal fluid might properly be questioned since symptoms and signs in these cases were confined to isolated involvement of a single cranial nerve, or a neuroretinitis

Spirochetes have been found in the cerebrospinal fluid in cases of acute syphilitic meningitis by Nichols and Hough (1913), Reasoner (1916), Wile (1917), Bly (1918) Joers (1920), Kemp and Chesney (1925), and Cioncas (1929)

Treatment and immediate results   The immediate prognosis is good, provided the treatment is instituted   Most of the fatalities in the literature occurred during the period (1910–1920) when arsenical therapy was thought to be contra-indicated   If the cases are treated by lumbar puncture and by intravenous injections of an arsenical drug (salvarsan, neosalvarsan, or tryparsamide), the immediate prog-

nosis is good   Moore (1929), does not record any deaths in his 81 cases and there were no immediate fatalities in Rothschild's (1927) series.   In our series of 80 cases there was one death   This came as the result of a subdural hemorrhage following a decompression operation   Operative intervention should not be necessary in these cases as the intracranial pressure can be controlled by lumbar puncture and, if needed, by intravenous injections of hypertonic solutions of glucose

Although the immediate prognosis is good in acute syphilitic meningitis, the cranial nerve palsies may persist   This is particularly true in cases in which the eighth nerve is involved   We have also seen persistent paralysis of the third nerve, and hemiatrophy of the tongue as a result of twelfth nerve involvement   We have recently seen a case, not included in this series, which had, in 1931, an acute syphilitic meningitis of the basilar type with bilateral seventh nerve palsy and right eighth nerve paralysis   The patient now shows complete deafness in the right ear, and weakness of the muscles of both sides of the face   When the patient eats there is a profuse lacrimation from both eyes ("crocodile tear" syndrome by Ford (1933)) Also, the convulsions which had their onset with the meningeal reaction may continue throughout the life of the patient even though all other signs of syphilis are eliminated   This may bear some reference to the incidence of convulsions in congenital syphilitics   In our experience the prognosis is best in the cases showing symptoms of an acute hydrocephalus without evidence of involvement of the cranial nerves or the meninges over the vertex   Greenfield and Stern (1932), however, report cases of chronic hydrocephalus in adults as a result of syphilitic meningitis and they suggest that some of the milder forms of hydrocephalus in infants may be due to a syphilitic infection

Pathology.   Pathological findings have been reported by Strassman (1910), Fahr (1914), Krause (1915), Wilson and Gray (1917), Neumann (1918), Graf (1918), Loeb (1918), Leitch (1918), Pirillae (1919), Staemmler (1921), Nonne (1921 and 1924), Ledarte (cited by Nonne 1921), Pette (1924), Spatz (cited by Pette 1924), Margulis (1926) and Lehoczky (1932)   One of the cases in this series was studied at autopsy

Grossly, these cases show only a slight clouding and thickening of the meninges at the base of the brain and over the convexities   Micro-

scopically the findings in these cases are those of a non-specific menin-geal reaction to the spirochetal invasion, namely an infiltration of the meninges with lymphocytes, occasional plasma cells, and polymor-phonuclear leucocytes   There is some perivascular infiltration of the superficial vessels of the cortex and the vessels of the basal ganglia The vessels of the meninges may show peri- and endarteritis   Occa-sionally small areas of softening as the result of vascular occlusion have been found in the cortex, and it is postulated that the sudden on-set of some of the cranial nerve palsies particularly that of the eighth nerve, are due to an endarteritis and thrombosis of the artery of these nerves   Spirochetes have been found in the meninges by Leitch (1918), Nonne (1921), Pette (1924), and Pinllae (1919)

Differential diagnosis   The chief differential diagnosis in acute syphilitic meningitis lies between the acute purulent meningitides and the meningitides due to the tubercle bacillus and the pathogenic yeast organisms, particularly the torula group   Tumor or abscess of the brain may produce a syndrome very similar to acute syphilitic meningitis

Acute purulent meningitis and tuberculous meningitis   The differen-tial diagnosis from acute bacterial meningitides depends on the results of the study of the cerebrospinal fluid   A frankly purulent cerebro-spinal fluid (several thousand cells with a polymorphonuclear pre-dominance) is extremely rare in acute syphilitic meningitis, and the finding of pyogenic bacteria on smear or culture establishes the diag-nosis   The differential diagnosis between acute syphilitic and tu-berculous meningitis is often much more difficult since the cerebro-spinal fluid findings are very similar, i e , a moderate pleocytosis (100 to 1000) with a lymphocytic predominance   A low glucose content in the fluid is no aid in the differential diagnosis as it may be present in either condition   The most valuable cerebrospinal fluid findings in the differentiation of syphilitic and tuberculous meningitis are the Wassermann reaction, the colloidal gold reaction, the chloride content, and the results of a stained smear   If acid-fast organisms are found on stained smears, the diagnosis of tuberculous meningitis is estab-lished   In almost every instance the occurrence of a positive Wasser-mann reaction in a meningitic fluid means that the meningitis is syphilitic   We have, however, seen several necropsy-proven cases

of tuberculous meningitis which had a positive blood and a positive cerebrospinal fluid Wassermann reaction   These were patients with systemic syphilitic infection   The positive spinal fluid Wassermann in these cases was due to the passage of the syphilitic reagin from the blood into the cerebrospinal fluid with the inflammatory exudate as described by Jahnel (1915), as no evidence of syphilis of the central nervous system was found   Occasionally weakly positive spinal fluid Wassermann reactions occur in cases of tuberculous meningitis which are thought to be a non-specific reaction, but are most probably due to errors in laboratory technique, as repeated tests will give negative results   The cerebrospinal fluid chlorides are a very valuable aid in the differential diagnosis in these cases, as we have never seen a cerebrospinal fluid chloride below 625 mgm per 100 cc in acute syphilitic meningitis, whereas figures much lower than this are frequent in tuberculous meningitis (Fremont-Smith'and Merritt, 1934).

Infections of the central nervous system with the yeast organism torula The clinical picture and cerebrospinal fluid findings in these cases are very similar to those of tuberculous and syphilitic meningitis   We have seen 3 necropsy-proven cases of torula meningitis in which the cerebrospinal fluid Wassermann reaction in the fluid was weakly positive, in 2 cases this was considered to be a non-specific positive reaction since subsequent tests were negative   One case was a known neurosyphilitic patient who developed a torula meningitis   The differential diagnosis in these cases depends on finding the yeast organisms in smears or growing them on Sabouraud's culture medium

Brain tumors   The symptomatology and clinical findings in the acute hydrocephalus group and the vertical group of acute syphilitic meningitis are very similar to those of brain tumor   The triad of headache, vomiting, and choked disc which is present in most of the cases of acute syphilitic meningitis, are symptoms classically associated with brain tumors   In the 'basilar group, the combination of paralysis of the nerves that have their origin in the cerebello-pontine angle may simulate tumors in this region as noted by Nonne (1924), Minz (1930), Friedman, Brock, and Denker (1933)   The history of the development of the symptoms is of considerable aid since the symptoms develop more rapidly in acute syphilitic meningitis than in brain tumor The differential diagnosis in such cases depends finally upon the re-

sults of the lumbar puncture   This is necessary since a considerable portion (26 per cent) of the cases of acute syphilitic meningitis do not give a history of primary or secondary infection, and a large number (40 per cent) have a negative blood Wassermann reaction   We have no doubt that some of the cases of so-called arachnoiditis reported chiefly from neurosurgical clinics, where lumbar punctures are not performed, are cases of acute syphilitic meningitis   We realize the danger inherent in lumbar puncture in cases suspected of brain tumor, but our experience, as well as that of others, is that lumbar puncture, if carefully performed, carries a very minimal risk   The examination of the lumbar fluid is of primary importance since Weigeldt (1923) and Ayer and Solomon (1925) have shown that the ventricular fluid may have a negative Wassermann reaction while the lumbar fluid will show a markedly positive reaction

Brain abscess   Acute syphilitic meningitis may occasionally simulate brain abscess and the spinal fluid finding in the two syndromes may be superficially quite similar   Clinically, brain abscesses may be distinguished from syphilitic meningitis by the absence of a history of syphilis, and by the presence of a septic focus such as an acute mastoiditis   The cerebrospinal fluid Wassermann and the progress of the case under treatment should decide the diagnosis

Other conditions   Occasional cases of post-diphtheria paralysis of the cranial nerves may offer some difficulty, but the history and lumbar puncture will give the diagnosis   We have also seen cases of nonspecific infectious polyneuritis as described by McDonald and Taylor (1932), in which the cranial nerves were first affected   The symmetry of the cranial nerve involvement in these cases is unusual in syphilitic meningitis, but the cerebrospinal fluid findings are usually necessary to establish the correct diagnosis   Cranial nerve palsies due to osteomyelitis and extra-dural abscess at the base of the brain sometimes occur and may simulate syphilitic meningitis   The presence of a draining ear or of mastoid disease is practically always present in these cases, however

Treatment   It is generally agreed that the most satisfactory immediate treatment of acute syphilitic meningitis should be vigorous anti-luetic therapy, using a combination of an arsenical drug with one of the heavy metals in some form   Some authors feel that ars-

phenamin is the drug of choice, but in most clinics neoarsphenamin is used on account of its simplicity of administration   We have had good results with the intravenous use of neoarsphenamin, 0 6 to 0 9 gram, depending on the size of the individual, administered every five days, accompanied by the intramuscular injection of a bismuth preparation If the intracranial pressure is elevated, it should be kept at a normal level by repeated lumbar punctures until the cerebrospinal fluid circulation is readjusted   Under such a routine, the patient should be sufficiently improved to be discharged from the hospital in fifteen to thirty days   It is probably wise to keep patients in the hospital for at least this length of time as it is often difficult (and requires close cooperation with social service workers) to get the patient to return to the out-patient department for further therapy   If cases are inadequately treated before discharge from the hospital, the whole syndrome may re-cur   After discharge from the hospital, the patient should be treated continuously for at least one and a half to two years, depending on the results of frequent blood tests and cerebrospinal fluid Wassermann examinations   The treatment in the ambulatory or outpatient clinic should consist of alternating courses of an arsenical drug (ten to twenty injections) given at weekly intervals, followed by intramuscular mercury or bismuth (eight to fifteen injections) given at weekly intervals   During the first six months after the acute meningitis we prefer to use neoarsphenamin (or arsphenamin) since it has been shown by Solomon (1933) that tryparsamide alone may not be effective in curing or preventing systemic manifestations of syphilis After six months tryparsamide may be substituted for neoarsphenamin   If at the end of a year and a half or two years of persistent treatment the cerebrospinal fluid is still markedly abnormal, the case should be considered as a "potential paretic" and a course of fever treatment (malaria or diathermy) should be given

Intraspinous and even intraventricular therapy has been used in these cases but we do not feel that the results are any more favorable and the economic considerations are greatly in favor of the simpler treatment outlined above

Final results   The treatment in our cases after discharge from the hospital has been quite varied   It has been the comment of previous

observers, and it is also our experience, that in spite of the dramatic symptoms presented by these patients, it is extremely difficult to get them to follow their treatment after discharge from the hospital, and even with the aid of intensive social service work more than one-half of the patients do not receive sufficient treatment   The statistics in the literature are, therefore, very inadequate as to the ultimate outcome of these cases

Since parenchymatous neurosyphilis may develop twenty to thirty years after the initial infection, it is hardly possible for one observer to follow all of his cases to a final outcome, and even when these patients are reexamined two or more years after the meningitis and are found to be symptom-free and serologically negative, it cannot be said that these patients are cured   It is extremely unlikely, however, that such cases later will develop dementia paralytica or tabes dorsalis as shown by the statistics of Altmann and Dreyfuss (1913) and Hopkins (1931)

There are two other series (Rothschild, 1927, and Moore, 1929) of cases in the literature in which the results of follow-up are reported in detail, and Nonne (1924) reports the results in 82 cases   Rothschild (1927) followed 34 cases for periods varying from three to twelve years Twenty cases received good treatment, and the cerebrospinal fluid became normal, all of the patients were "clinically cured" at the end of the period of observation, although only 5 had a lumbar puncture at this time   Fourteen cases received poor treatment   Three of these cases were "clinically cured" and had normal cerebrospinal fluids   All of the remaining 11 cases had abnormal cerebrospinal fluids at the end of the period of observation   In 3 of them tabes dorsalis developed, in 3 others dementia paralytica, and in 1 case optic atrophy in the left eye   In one of the remaining cases the outcome was doubtful   Three cases died one, three, and five years after their admission to the hospital   In none of these 3 cases was there any definite evidence of a syphilitic meningitis as none of the cases had a positive blood or cerebrospinal fluid Wassermann, nor were the clinical syndrome or the other cerebrospinal fluid findings characteristic of syphilitic meningitis   An autopsy was performed in 2 of the cases that died   In case 7, there was a large hemorrhage in the left thala-

mus, and shrunken kidneys   In case 8, the objective examination of
the brain was negative.   In this case the clinical picture was typical
of disseminated sclerosis.

Moore (1929) followed 28 cases for periods varying from one to nine
years   Fourteen cases received good treatment.   Ten cases had
normal cerebrospinal fluids and were clinically cured   Two cases de-
veloped dementia paralytica, and in 2 cases the cerebrospinal fluids
remained abnormal, although they were symptom-free and the neuro-
logical examination was normal   Fourteen cases received poor treat-
ment   Seven cases had normal cerebrospinal fluids and were "clini-
cally cured."   One case developed dementia paralytica   Six cases
had persistently abnormal cerebrospinal fluids and positive findings on
neurological examination without mental changes

Nonne (1924) reports the results in 82 cases in percentages, without
giving the period of observation or amount of therapy   He records
good results in 70 per cent and poor results in 30 per cent

Thirty-eight of our cases were followed for periods varying from
two to sixteen years   The final serological status was not obtained in
6 of these cases, and they are, therefore, excluded, although they were
symptom-free and the neurological examination was normal   Twenty-
five of the remaining 32 cases were considered to have received good
treatment after the meningitis (at least one and a half to two years of
continuous treatment)   Twenty-one of these 25 were "clinically
cured" and serologically normal, in 1 case dementia paralytica de-
veloped, in 1 there was persistent third nerve palsy with right-sided
optic atrophy and persistent abnormalities in the cerebrospinal fluid,
2 cases were symptom-free and the neurological examination was nor-
mal but the cerebrospinal fluid showed persistent abnormalities
(asymptomatic neurosyphilis).

Seven cases received poor treatment   One case was clinically re-
covered and serologically normal, in 1 tabes dorsalis developed, in
another dementia paralytica, and 1 case died two years after the
meningitis with a hemiplegia and dementia, but autopsy was not
permitted.   One case showed Argyll Robertson pupils and slight men-
tal changes six years after the meningitis   The cerebrospinal fluid
findings were characteristic of dementia paralytica, and in 2 cases
there were persistent slight abnormalities in the cerebrospinal fluid,
although they were symptom-free and neurologically normal

Table 17 shows the results in 91 cases of acute syphilitic meningitis as compiled from our series, and those of Rothschild and Moore Rothschild's 3 doubtful cases are not included in this series   This table shows that a clinical recovery was obtained in 51 of the 59 cases (87 per cent) that received good treatment, which is in striking contrast to the figures in the group that received poor treatment, 11 out of 32 cases (34 per cent)   These figures show conclusively that early syphilis of the meninges does not protect the individual from parenchymatous neurosyphilis as claimed originally by Mattauschek (1926)   They also show that the prognosis with good treatment is very good (87 per cent recovery)

TABLE 17

The final status in 91 cases of acute syphilitic meningitis

	FINAL STATUS AFTER							
	Good treatment				Poor treatment			
		Developed					Developed	
SERIES OF	Re-covered	Tabes dorsalis	De-mentia para lytica	Other types of neuro-syphilis	Re-covered	Tabes dorsalis	De-mentia para lytica	Other types of neuro-syphilis
Rothschild	20	0	0	0	3	3	3	2
Moore	10	0	2	2	7	0	1	6
Authors	21	0	1	3	1	1	1	4
Total	51	0	3	5	11	4	5	12

VI SUMMARY

1 Acute syphilitic meningitis is a relatively rare complication of syphilis as it occurs in less than 5 per cent of the cases   It usually occurs in young adults but it may be a complication of congenital syphilis   The meningeal symptoms usually develop within one year of the primary infection, but it may develop at any time after the initial lesion and it may be a complication of parenchymatous neuro-syphilis   The symptoms have an acute or subacute development In most instances they are present two to four weeks before the patients seek admission to the hospital   The meningitis is not caused or precipitated by arsenical therapy   Thirty-six per cent of our cases had no anti-luetic therapy prior to the onset of the meningitis, and the

onset of meningeal symptoms did not occur in any of our patients while they were receiving arsenical therapy, nor have we found any case recorded in the literature in which the symptoms developed during arsenical therapy   They may develop, however, while the patient is receiving mercury by inunction or intramuscular injection

2   Clinically the cases divide themselves into three groups according to the presence of symptoms indicating involvement of the meninges in various regions of the brain as follows   (1) acute syphilitic hydrocephalus, cases with headache, nausea and vomiting, choked discs and meningeal signs (stiffness of the neck and Kernig's sign) indicating involvement of the meninges in the posterior fossa interfering with the circulation of the cerebrospinal fluid and causing the development of an acute hydrocephalus, (2) acute vertical meningitis, cases with headache, nausea and vomiting, convulsions or mental symptoms indicating involvement of the meninges over the vertex of the brain, (3) acute basilar meningitis, cases with cranial nerve palsies indicating involvement of the meninges at the base of the brain

3   The blood Wassermann test is positive in only 60 per cent of the cases and is an unreliable test in excluding the diagnosis of acute syphilitic meningitis   The cerebrospinal fluid findings are characteristic, and the diagnosis can be immediately established only by lumbar puncture   The cerebrospinal fluid is usually under increased pressure, which may be as high as 600 to 700 mm   There is moderate or marked pleocytosis (25 to 2000 cells per cubic millimeter)   Lymphocytes are the predominating cell type but 5 to 15 per cent polymorphonuclear leucocytes are usually present and rarely they may predominate The protein content of the fluid is increased   The glucose content may be normal or decreased (18 to 84 mgm per 100 cc)   The chloride content is usually normal or only slightly decreased (636 to 742 mgm per 100 cc)   The colloidal gold reaction is practically always abnormal and may be of any type   A mid zone curve is found in 50 per cent and a first zone in 40 per cent   The cerebrospinal fluid Wassermann is positive in approximately 90 per cent   Spirochetes have been found in the fluid

4   The pathological findings are a non-specific reaction to the treponema pallidum   The meninges are infiltrated with lymphocytes, plasma cells and occasionally polymorphonuclear leucocytes   There is a slight degree of perivascular infiltration of the meningeal and

superficial cortical vessels   Occasional small areas of cortical soften-
ing are found as a result of thrombosis of vessels showing peri- or en-
darteritis

5   The treatment of acute syphilitic meningitis consists in the in-
travenous injection of arsphenamine (or its derivatives) and frequent
lumbar punctures   Under this treatment the acute symptoms rapidly
subside   The ultimate prognosis is good (87 per cent) when the proper
follow-up treatment is given   The prognosis is poor (34 per cent)
when no treatment or inadequate treatment is given   Parenchymat-
ous neurosyphilis (tabes dorsalis and dementia paralytica) may de-
velop as a sequel to acute syphilitic meningitis [2]

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PRESENT DAY STATUS OF LIVER FUNCTION TESTS

LOUIS J SOFFER, M D

WITH THE ASSISTANCE OF FLORENCE BARCLAY WHITE, A B

From the Department of Medicine of the Johns Hopkins University School of Medicine

CONTENTS

I Physiological Considerations

A Bile Pigment Metabolism

Ever since the identity between hematoidin and bilirubin was suggested, extensive data have accumulated to demonstrate that bile pigments are formed from hemoglobin   The question whether the hemoglobin presents the only source of bile pigment has been the subject of a good deal of investigation   Whipple and Hooper (1, 2) have presented evidence which they believe favors the theory that sources other than hemoglobin exist for the manufacture of bile pigments   They demonstrated the fact that if a diet rich in carbohydrates was fed to dogs with bile fistulae, the amount of bilirubin excreted by the liver was greatly increased   They further found that dogs with an Eck-fistula do not excrete as much bilirubin as do normal dogs   From these observations they concluded that the liver cells are capable of making bile pigment from substances other than hemoglobin, and that the diminution in excretion of bilirubin in Eck-fistulae animals was due to disturbances in the function of liver cells resulting from the operative procedure, all of which indirectly suggested the importance of the liver cells in the manufacture of bilirubin   These observations of Whipple and Hooper, although impressive at first glance, are subject to several criticisms which definitely invalidate the conclusions of these workers   Rous, Brown, and McMaster (3) and Inlow (4) showed that in such experiments if the bile is collected over a 24-hour period rather than during the 6–8 hour period used by Whipple and Hooper, the feeding of large amounts of carbohydrate did not result in an average increase in the amount of bilirubin excreted by the liver   The Eck-fistula experiments are open to the criticism that, since the nature of the operative procedure is such as to divert the larger portion of the blood supply of the liver the amount of bilirubin brought to it for excretion might be proportionately less

Brown, McMaster and Rous (5) who studied the question of the origin of bile pigments carefully, concluded that their data supported the theory that bilirubin has no sources other than the hemoglobin of destroyed blood   Rich (6) presented direct microscopic evidence to demonstrate this point   He studied in vitro cultures of red cells and phagocytes, and could see the formation of bilirubin crystals within the body of the phagocytes as the red cells were ingested and destroyed

It would seem that the evidence is overwhelming in favor of the theory that bile pigment is produced from the blood hemoglobin Whether this is the only source is still questionable   Whipple (7) presented evidence to show that muscle hemoglobin is a source of bilirubin formation

The next question that arises concerns itself with the relation of the liver to the actual manufacture of bile pigment   Rich (8) quotes that Morgagni, who taught as early as the seventeenth century, believed that the liver serves merely as an excretory organ for the bile brought to it from the blood   It was not until the beginning of the twentieth century, however, that the problem was subjected to careful scientific scrutiny   In the latter part of the nineteenth century it was universally assumed that the epithelial cells of the liver manufacture bilirubin   On the basis of the fact that the tumor cells of primary liver cell carcinoma contain bilirubin, Lubarsch (9), as late as 1921, was led to conclude that the epithelial cells undoubtedly can produce bile pigment   From the conclusion of Tarschanoff (10) and others (11, 12, 13) that the liver cells possess tremendous ability to remove bile pigment from the blood stream as part of the excretory function it would seem not at all surprising to find this pigment in liver cell carcinomata

The theory that the epithelial cells of the liver formed bilirubin received great impetus and support from the widely quoted experiments of Minkowski and Naunyn (14)   They found that intravascular hemolysis produced by arseniuretted hydrogen produced intense jaundice in normal ducks and geese while in hepatectomized fowl no jaundice appeared after such hemolysis   This seemed to prove definitely the important, if not primary, role that the liver plays in the production of bilirubin   However, in the light of our present knowledge which is the outgrowth of the work of Lowit (15) and of McNee (16, 17) particularly, both of whom established the importance of the reticulo-endothelial system throughout the body in the manufacture of bilirubin, the absence of jaundice in Menkowski's and Naunyn's hepatectomized fowl could readily be explained   McNee (17) pointed out that removal of the liver removes the kupfer cells which in birds constitute the bulk of the reticulo endothelial system

The ultimate proof of the extrahepatic formation of bile pigment

was finally provided by the work of Mann, Bollman, and Magath
(18)   Mann (19) devised an operative procedure whereby the liver
could be completely extirpated from the dog without interfering with
the circulation through the rest of the body   In such hepatectomized
animals Mann, Bollman, and Magath (19) reported that the bile pig-
ment appears in the plasma (in dogs it is normally absent) within 3 to 6
hours after the hepatectomy, and increases in amount until the animal
dies   The intravenous injection of hemoglobin hastened and increased
the amount of bile pigment formed   They further showed that such
increase in bile pigment in the circulating plasma would appear even
though all the abdominal viscera were removed   This work was sub-
sequently confirmed by Rich (20) and Markino (13)   Mann, Sheard
and Bollman (21) then attempted to determine the site of maximum
formation of bilirubin   They studied spectrophotometrically the
amount of bile pigment produced by the various abdominal and extra-
abdominal organs after total hepatic extirpation in the dog, and they
concluded that most of the bile pigment is manufactured by the
reticulo-endothelial cells of the bone marrow while only relatively in-
significant quantities are produced by the liver and spleen. Subse-
quent investigations, however, tended to throw a good deal of doubt
on the conclusions of Mann, Sheard and Bollman   Matthieu (22)
showed that the spectrophotometric curves published by Mann et al
(21) differed essentially from similar control curves of bilirubin solu-
tions   This difference is apparently due to another pigment and
Matthieu concludes that the evidence presented by Mann and his
co-workers does not necessarily prove that the bone marrow is the
essential organ concerned with the production of bile pigment   More
direct evidence was produced by Ascoli, Fioretti, and Malago (23)
They made simultaneous determinations of the bilirubin content of the
arterial and venous blood of various organs of the dog and they con-
cluded that the liver was the chief, although not the only site, of the
formation of bilirubin.

As a result of all this investigation, certain facts stand out rather
clearly   Certainly there is no evidence that the epithelial cells of the
liver are concerned in the manufacture of bilirubin. The evidence
that it can be made extrahepatically is conclusive   The site of this
formation is a matter of much less certainty   If the reticulo-endo-

thelial cells are actually concerned in the manufacture, then the kupfer cells of the liver which are present in enormous numbers, must be considered to play an important part   The function of the epithelial cells of the liver, in contrast to that of the kupfer cells, is to excrete into the bile canaliculi the bilirubin brought to it by the blood stream

In the light of these findings, any increase in the bilirubin in the circulating blood stream must be either an expression of the increased activity of the reticulo-endothelial cells such as occurs in the hyperbilirubinemia of hematogenous origin, an indication of the decreased excretory ability of the hepatic epithelial cells, or a manifestation of obstruction of the bile ducts   Normally the excretory function of the liver cells keeps pace with the destruction of the red blood cell and the blood bilirubin is maintained at a fairly constant level   Where blood destruction is unusually active the liver threshold for bile pigment is exceeded and hyperbilirubinemia results   This represents one phase of the relationship of the excretory power of the liver cells to the amount of bile pigment formed   Here the fault lies extrahepatically   The other phase is represented by the disease processes of the liver in which the amount of bile pigment normally formed is incapable of being handled by the liver cells and an increase in the bilirubin content of the blood follows   The various tests which enable us to distinguish between the types of hyperbilirubinemia will be discussed subsequently

The further stages dealing with the metabolism of the bile pigments are concerned with the changes that occur in the intestinal tract   The bilirubin which is excreted by the liver cells into the bile canaliculi finds its way through the main bile ducts into the intestine   In the stool most of the bile pigment is present as urobilin   How this transformation occurs is still somewhat uncertain   Muller (24) found that urobilinogen could be formed by the addition of putrefactive bacteria to bilirubin in peptone solution   Somewhat later Beck (25) obtained similar results by treating bilirubin with various strains of bacteria Ladage (26) administered bilirubin by mouth and obtained a marked increase in the urobilin content of the stool and a slight but definite increase in the urine   On giving 100 miligrams of urobilin by mouth he obtained a pronounced increase in urobilinogen in the urine

The evidence, as presented, indicates that the bilirubin is in all

probability acted upon by the bacteria in the large intestine with the formation of urobilinogen which is excreted for the greater part in the stool and on exposure to light and air is converted into urobilin   That the urobilinogen content of the urine was increased on the oral administration of urobilin points to the fact that the urobilinogen is absorbed from the intestinal tract through the portal circulation   Wallace and Diamond (27) believe that some of the absorbed urobilinogen is further acted upon by the liver and reconverted into bilirubin while the rest is excreted as urobilinogen through the kidneys   The amount normally found in the urine of man according to these authors rarely exceeds a 1 20 dilution

The chemical reaction involved in the transformation of bilirubin into urobilinogen is one of reduction   Disque (28) showed that by strong reduction of bilirubin with sodium amalgam and other reducing agents, the chromogen of urobilin, urobilinogen could be obtained By subsequent oxidation the urobilinogen could be converted into urobilin

The amount of these reduced bile pigments found in the urine and stools is used as a test for liver function

B THE RELATIONSHIP OF THE LIVER TO THE EXCRETION OF DYES

The injection of certain dyes intravenously is now widely used as a method for determining the functional status of the liver   Considerable improvement in this particular method followed the original work of Abel and Rowntree (29) in 1909, who observed that phenoltetrachlorthalein injected into the blood was excreted almost entirely by the liver and appeared in the bile   Rowntree, Hurwitz and Bloomfield (30) developed a functional liver test depending on the stool content of the injected phenoltetrachlorthalein   At about the same time Whipple, Mason and Peightal (31) demonstrated that the rate of elimination of this dye was proportionate to the degree of hepatic injury which they produced by the use of chloroform, hydrazine, and phosphorus   Rosenthal (32) injected phenoltetrachlorthalein intravenously in normal dogs, and in dogs in which the liver had been injured by exposure to prolonged chloroform anaesthesia, and determined colorimetrically the concentration of the dye in the blood stream at varying intervals   He suggested that the test could be employed clinically as a quantitative test for liver function

Somewhat later, Rosenthal and White (33) compared the rates of excretion into the bile of rabbits of various chlorine, bromine and iodine compounds of phenol, cresol and resorcinol-phthalein dyes Of all these dyes the sulphonated phenoltetrahalogen phthalein group was found to be most satisfactory Sixty to 90 per cent of the injected dyes were excreted in the bile of normal rabbits within one hour after the injection of 5 mgm per kilogram of body weight After production of liver injury the disappearance of the dyes from the blood stream proceeded very slowly Of this group of dyes bromsulphalein (phenoltetrabromthaleinsulfonate) was found to be most satisfactory, as it is retained almost in toto shortly after the injection and because it disappears quite slowly from the blood stream After injection the non-sulfonated dyes like phenoltetrachlorthalein disappear from the blood almost entirely This is probably due to the fact that a large portion of the dye diffuses into the tissues Later the dye is collected, carried to the liver and excreted This occurs both in normal animals and in animals where liver injury has been produced The sulfonated dyes, on the other hand, even in the presence of liver disease, do not diffuse into the tissues From 80 to 100 per cent of the dye can be recovered from the blood stream shortly after injection and later it is almost entirely excreted by the liver The difference in behavior between these dyes is probably due to the fact that the colloidal phenoltetrachlorthalein is insoluble as it circulates in the blood stream and, as was shown by the very early work of Aschoff, Ribbert, Goldman and Kyona, colloidal dyes behave like finely particulate matter and are removed from the blood stream by the reticulo endothelial system Sulfonation of the tetrahalogenthalein dyes renders them soluble and hence they are probably taken up but little if at all by the phagocytic cells

Such dyes as tetraiodophenolthalein and tetrabromphenolthalein are unsatisfactory for quantitative studies because of the weakness of their color Rosenthal and White (33) injected 50 mgm intravenously into rabbits but could not demonstrate the dye either in the bile, the urine, or the blood serum It may be that these dyes are taken up entirely by the reticulo endothelial cells or possibly if they are excreted by the channels previously mentioned they are in a colorless form the color of which cannot be restored either with alkalies or acids

Pratt et al (34) showed that after blocking the hepatic circulation completely by ligating the hepatic blood vessels and anastomosing the portal vein and inferior vena cava, the excretion of intravenously injected bromsulphalein is almost negligible while in perfectly normal dogs the dye disappears rapidly from the blood stream They found that the average retention of the dye in normal dogs was 64 per cent the first minute and 3 per cent the tenth This is interpreted as further evidence that the dye is excreted specifically by the liver Herlitz (35), on the other hand, suggested that bromsulphalein might be excreted through the reticulo-endothelial cells, particularly through the kupfer cells of the liver More positive evidence recently appeared in the work of Klein and Levinson (36) They injected bromsulphalein intravenously in the dosage of two miligrams per kilogram of body weight, into dogs which had been splenectomized and they found that splenectomy causes a slight but definite slowing of the removal of the dye from the blood stream They then blocked the reticulo-endothelial system with india ink injections and found that considerable retention of the injected dye followed. Their conclusions were similar to those of Herlitz (35) who showed that bromsulphalein is excreted through the reticulo-endothelial system, the kupfer cell component of which probably plays an important rôle This is somewhat similar to the evidence produced by Shellong and Eisler (37) who found that such dyes as phenoltetrachlorthalein and Ascorbin-S were removed from the blood by the entire reticulo-endothelial system Rosenthal and Lillie (38) repeated their experiments and found that splenectomy or blockage of the reticulo-endothelial apparatus with quartz does not alter the rate or degree of removal of the bromsulphalein from the blood

We must consider one other important dye in this discussion, namely, rose bengal (tetraiodotetrabromfluorescene) Delprat (39) conducted experimental studies with this dye It is a crystalloid and is non-toxic to the animal organism in fairly large doses He studied its rate of disappearance from the circulation of normal dogs and then again in these same animals after they had been subjected to prolonged chloroform anaesthesia He found that the elimination of rose bengal from the circulation was profoundly influenced by liver injury. In order to determine the rate and extent of elimination of this dye in the

bile of a normal dog, he injected 30 mgm into the circulation and collected the bile for 5 hours   Thirteen milligrams of the injected dye were thus recovered   The dye however is present only in very small amounts in the blood stream after 16 minutes   It would seem then that rose bengal is not immediately excreted by the liver but is previously removed from the circulation through some other agency and then is excreted by the liver into the bile passages   None appears in the urine

Today the dyes most frequently used to determine liver function are bromsulphalein and rose bengal   In the absence of obstruction to the bile passages these dyes are excreted by this organ specifically although perhaps not quantitatively   There is some evidence to show that the reticulo endothelial cells are capable of taking up bromsulphalein   Similarly, the disproportion between the rate of disappearance from the circulation of the rose bengal and its appearance in the bile suggests that here too the phagocytic cells may play a rôle   This unknown intermediary factor probably accounts for the diverse results that are not infrequently obtained with the use of these dyes   Their appearance in the urine occurs only when hepatic damage is very extensive or when obstruction to the bile passages occurs and their presence in the blood stream is unduly prolonged   These dyes test specifically the excretory function of the liver parenchymal cells although it must be remembered that retention of the dye will occur with obstructive lesions of the bile ducts in the presence of normal liver cells

C   METABOLISM OF BILE ACIDS

The quantitative estimation of bile acids as a means of determining the functional status of the liver has never been widely employed because of the attending technical difficulties   These acids are present in the blood in such minute quantities that their detection is difficult and uncertain   Clinically we have limited ourselves essentially to qualitative analysis of bile withdrawn through a duodenal tube   What accurate information we have gathered has been the result of studies conducted on bile obtained from bile fistulae in experimental animals   The fact that the estimation of these acids clinically has been so limited is unfortunate since they are perhaps the only con-

stituents of bile that, in all probability, are manufactured exclusively by the liver

Smyth and Whipple (40) working with Eck-fistula dogs showed that minute doses of chloroform are capable of effecting a pronounced decrease in the bile salt concentration of fistula bile   Similarly phosphorous, in larger doses, affects the output of these elements   Both of these drugs are notorious hapatic poisons affecting mainly the parenchymal cells of the liver   Mann and Magath (41), on the other hand, demonstrated a positive Pettenkofer reaction on the blood serum of hepatectomized dogs   This evidence was advanced in favor of the extra-hepatic genesis of bile acids   Their observations lend themselves to one serious criticism which Jenke (42) has rightly emphasized, which is the failure of the authors to examine the serum spectroscopically   As early as the middle of the last century workers like Muller, Kunde, and Moleschot could demonstrate no definite Pettenkofer reaction in the blood, lymph, tissues, or urine of frogs which had been hepatectomized, many of their frogs survived for as long as 21 days

Evidence of a more suggestive nature concerning the hepatic origin of bile acids was presented by Jenke and Steinberg (43)   They found that although the liver excretes about 10 grams of bile acids daily, the amount present in the blood stream did not exceed 0 025 mgm per cent   Tashiro (44), Gregory and Pascoe (45) as a matter of fact found none in the general circulation   In view of the marked discrepancy that exists between the amount of bile acids present in the bile and the amount in the blood stream, it would appear unwarranted to suppose an extra-hepatic site of origin   Similarly in obstructive jaundice these authors found that an increase in the bile acid content of the blood and a spilling over into the urine occurs only directly after the obstruction has been produced   After prolonged obstruction to the bile passage the bile acids of the blood quickly decrease although the jaundice becomes more intense   The explanation probably resides in the fact that because part of the total bile pigment is manufactured extra-hepatically, the bilirubin will continue to accumulate in the blood in the presence of biliary obstruction, the manufacture of bile acids, on the other hand, will be minimal due to the hepatic parenchymal changes secondary to blocking of the biliary passages   The

extensive work, too, of Smith and Whipple (46) tends to show the primary part that the liver plays in the manufacture of these elements

There is a certain amount of evidence which tends to indicate that the kupfer cells of the liver, in addition to the epithelial cells, play some rôle in the formation of bile acids   Thus, Makami (47) blocked the reticulo-endothelial system with india ink, electrolgol, and lithiocarmine and found that the bile salt concentration in the bile of dogs with gall bladder fistulae was somewhat reduced

In view of the fact that the liver plays such an important and primary rôle in the manufacture of these acids one might expect that their quantitative determination would constitute a sensitive means for determining liver function   Practically, this is not true for several reasons aside from the purely technical difficulties usually encountered The ability of the liver to manufacture bile acids in normal quantities is maintained intact up to the end stages of liver disease except where the hepatic parenchymal damage is very extensive as it is in acute yellow atrophy   Rosenthal and Zinner (48) determined the concentration of bile salts in the bile of patients with advanced atrophic portal cirrhosis and found no deviation from the established normal values   Another factor of great importance is the influence of diet on the excretion of bile acids   Thus, Foster, Hooper, and Whipple (49) found that the concentration of these substances could be increased considerably by the use of a meat diet, while a high carbohydrate diet tends to inhibit their concentration in bile   Smith and Whipple carried these experiments further and demonstrated the important effect that a large variety of substances exercised on the production of bile acids

D THE RELATION OF CARBOHYDRATE METABOLISM TO LIVER FUNCTION

We shall concern ourselves essentially with the relation of the metabolism of galactose and frustose to the liver, since these two sugars are the ones most extensively used as liver function tests

Strauss (50) at the beginning of this century introduced levulose for testing hepatic function and several years later Bauer (51) introduced galactose for a similar purpose   But it has only been within the past two decades or so that experimental evidence concerning the metabolism of these sugars has accumulated which has revealed the reasons for their peculiar adaptability for this purpose

Cori (52) studied the rate of absorption of hexoses and pentoses from the intestinal tract of rats, and found that only negligible quantities of sugar were lost through the action of the bacteria in the intestines   In comparing the rate of absorption of galactose, glucose, and fructose, he found that the first two proceed at about equal rates, a rate which is about 2 5 times as rapid as the absorption of fructose This is a very significant observation, if these sugars are to be utilized as tests by oral administration   It is rather interesting that despite the fact that the rate of absorption of glucose is much greater than that of fructose, the extent to which they are converted into liver glycogen within a given period of time is the same   Cori (53) found in the rat, that about 39 per cent of orally ingested glucose and fructose is converted into liver glycogen within 4 hours, while only 12 per cent of the galactose is converted during a similar period   If we take into consideration the differences in the rate of absorption of glucose and fructose, we find that only 17 per cent of the amount of the former is ingested while 39 per cent of the latter is retained as liver glycogen Following the same line of reasoning only about 5 per cent of the galactose is similarly retained   It becomes obvious that although fructose is readily converted into glycogen by the liver, galactose is so converted with difficulty and then in only relatively negligible quantities   This is an important point since the merits of the various carbohydrates as liver function tests depend essentially on their convertibility into glycogen

The extent to which a particular sugar is converted into glycogen probably determines the degree of hyperglycemia that results following its ingestion.   Thus, Foster (54) found that the ingestion of 40 to 100 grams of galactose produced a marked hyperglycemia in adults This is essentially what one might expect in view of the fact that the conversion of this sugar into glycogen occurs with such great difficulty and is so slight   Bodansky (55), studying the tolerance of dogs for fructose, glucose and galactose, confirmed the observations of Foster and found that galactose produced a marked hyperglycemia while fructose was much less effective than either glucose or galactose in raising the level of blood sugar   Both glucose and more particularly galactose will appear in the urine after ingestion of moderate quantities while glycosuria rarely occurs following the oral administration of

(64) found that 10 units of insulin injected after the oral administration of 40 grams of galactose caused only a slight diminution in the urinary excretion of this sugar in their patients despite the markedly lowered blood sugar   Roe and Schwartsman (63) further found no difference in tolerance for galactose between normal individuals and diabetics From these observations the probabilities are that the metabolism of galactose is essentially independent of the influence of insulin   This does not entirely hold for levulose although Cori quotes McCleod (66) as saying that a diabetic liver can convert levulose into glycogen which then becomes available as glucose to the organism   Cori (66) found that large doses of insulin almost completely suppress the formation of glycogen in the liver from both glucose and fructose   In contrast to this observation of Cori, Wierzuchowski (67) showed that maximal injections of insulin will not alter the tolerance to large quantities of levulose given through continuous intravenous injections

It would seem from these observations that the metabolism of galactose is influenced specifically by the liver   It is utilized apparently only very slightly if at all by the other tissues and its metabolism remains unaffected by insulin   Fructose, on the other hand, may be metabolized outside the liver   Although here it should be emphasized that the liver rapidly absorbs a large portion of the levulose which comes to it, so that the amount utilized by the muscles is normally very small   The effect of insulin on the levulose metabolism is a factor of no very considerable physiological significance   What part the other endocrine glands play in the metabolism of these sugars is still a problem that demands investigation

One further point to be discussed is the relationship of fructose and galactose to the renal threshold   Bauer (51) found that the tolerance of normal human beings for galactose is about 40 grams   Rowe (68) found that the tolerance varied in males and females, being somewhat lower in the males   He suggested that the mammary glands are capable of absorbing or utilizing galactose which thus raises the tolerance   Shay, Schloss, and Bell (64) investigated this point in 15 normal males and in an equal number of females of varying ages and weights   They concluded that no difference in tolerance existed

Folin and Berglund (56) who investigated the renal threshold for galactose found that no such threshold existed   This view was some-

what substantiated by the findings of Cori (53) who, by producing a tartrate nephritis in animals, could effect a complete retention of dextrose without altering the rate at which galactose disappeared from the blood stream   Rowe and Chandler (69) although admitting that some leakage of a reducing substance through the kidneys occurs after the administration of even small doses of this sugar, doubt that these reducing agents are galactose   However it may be, the extremely low renal threshold permits the utilization of the degree of glycosuria of galactose as a means of testing hepatic function   Fructose, on the other hand, has a renal threshold similar to that of glucose   This was demonstrated by Folin and Berglund (56) and by Bodansky (55) Because of this relatively high threshold, changes in the blood sugar following the administration of levulose are utilized as an index of liver function

E   MISCELLANEOUS PHYSIOLOGICAL CONSIDERATIONS IN RELATION TO LIVER FUNCTION

1 Detoxicating function of the liver

Within recent years the study of the detoxicating function of the liver has occupied the interest of both the physiologist and the clinician   That this organ plays some rôle in rendering many poisons innocuous there can be no doubt   To what extent other organs, notably muscle, are concerned in this process is still not very clearly understood   Priestly, Markowitz, and Mann (70) studied the rate of disappearance of strychnine injected intravenously into normal and hepatectomized dogs   They found that in normal animals four minutes after the injection of 50 mgm of strychnine, the concentration of this drug in the liver was more than seven times that in the blood   Later the strychnine content of the liver of these dogs was considerably reduced without any concomitant increase in its concentration in the blood stream   This would suggest that not only is this drug taken up by the liver but that it is probably destroyed there   In hepatectomized dogs the intravenous injection of strychnine was followed by a very gradual and comparatively slight fall in the concentration of the drug in the circulation   The moderate decrease of the strychnine content of the blood in these animals was accounted for by a proportionate accumulation in the muscles   It would seem from

the experiments of these authors, that, at least as far as strychnine is concerned, the liver plays not only an important, but a primary rôle in its removal and destruction

The destruction of cincophen too, has been assumed to be a property of the liver although Rotter (71) found no evidence of oxidation of cincophen by the dog's liver She suggested that the liver of animals differed from that of human beings in respect to their behavior toward this drug Lichtman (72) presented some indirect evidence by comparing the time of appearance and concentration of the oxidized form of cincophen in the urine and bile obtained by transduodenal drainage, that the liver plays an important part in its destruction Normally, after the ingestion of a given quantity of cincophen, part of it is excreted in the urine as oxycincophen (2-(ortho-hydroxy)-phenyl-quinoline-4-carboxylic acid) and the rest in some further oxidized state In patients with liver disease this author found that only simple oxidation to oxycincophen occurs so that the concentration of this substance in the urine is considerably increased

2 Deaminization of amino acids

The concentration of amino acids in the urine has been utilized as a test for hepatic function The basis of this test is dependent essentially on the rôle of the liver in the conversion of amino acids into urea In hepatectomized animals protein catabolism remains unaltered except for the fact that the amino acids formed as a result of protein breakdown are not deaminized These compounds accumulate in the blood and tissues and are excreted as such in the urine instead of being converted into urea as they are in normal animals Von Folkenhausen and Siwon (73) injected large quantities of amino acids into hepatectomized geese and found that the amount of ammonia excreted by these animals was greatly increased although no urea formation could be determined As a matter of fact the rate of ammonia formation was the same in the normal, as it was in the hepatectomized geese They concluded that the liver is not involved in all the phases of intermediary protein metabolism, but that the synthesis of urea seemed to be an exclusive function of this organ Bollman, Mann and Magath (74) studied the process of deaminization in completely hepatectomized dogs In these animals they found that no deaminization occurred This was demonstrated by the recovery in

the urine, blood, and tissues of amino acids in amounts about equal to the urea formation which would have been anticipated if these dogs had been normal   The quantity of amino acids injected was recovered completely and unchanged many hours after its administration   It would seem from their experiments that urea cannot be formed in the absence of the liver, while ammonia which continues to appear in the urine in hepatectomized animals is not derived from the amino acids, but rather represents some other phase of protein metabolism which is not dependent on the integrity of the liver   Very substantial contributions concerning the probable chemical mechanism whereby amino acids, most particularly ornithin, are converted into urea by the liver, were presented in a recent paper by Krebs and Henseleit (75)

II   LIVER FUNCTION TESTS

It is impossible to investigate critically the innumerable tests for liver function which have appeared in the literature during the past two decades, nor is there any particular need for such exhaustive studies   Most of them have failed to measure up to the exacting practical criteria and have gradually fallen into disuse   Some have survived and were found to be clinically useful, although here too, the claims of their individual enthusiasts were found to be exaggerated But in the course of time their field of usefulness and their limitations were fully realized, and they now occupy a definite place in the laboratory investigation of hepatic disease

No one test can be entirely satisfactory   The functions of the liver are too multiple and diverse to be measured by any one procedure Some of these functions are disturbed earlier than others, and it is only through the employment of a number of tests and through the study of various hepatic functions, that we may finally arrive at a satisfactory appraisal of the status of this organ

A   THE EXCRETION OF THE BILIARY ELEMENTS

1   Bilirubinemia

The determination of the degree of bilirubinemia is an important feature in the diagnosis of hepatic disease   Since the liver is so

intimately concerned, at least with the excretion of this pigment, one might expect that the amount of bilirubin circulating in the blood stream would reflect the functional state of this organ But it must again be emphasized that the excretion of bilirubin is only one of many functions of the liver and it is entirely compatible with our clinical results to find this particular function spared while some or all of the others are disturbed Even in those instances in which hyperbilirubinemia is present, the existence of actual liver disease is not necessarily established The presence of jaundice in the early stages of obstruction of the common duct, and the increase in the amount of circulating bilirubin that we meet with in patients with excessive blood destruction, are well known examples of hyperbilirubinemia without liver disease

Until the very beginning of the present century, the presence of an increase of bile pigment in the blood was made purely on the clinical observation of jaundiced skin and sclera Gilbert (76) and his associates were the first to elaborate a method for the estimation of serum bilirubin But it was not until van den Bergh and Snapper (77) adopted Ehrlich's diazo-reaction for the estimation of blood bilirubin that a satisfactory and fairly accurate method for this purpose was evolved Later Thannhauser and Anderson (78) further increased the sensitivity of the method by salting out the proteins with a saturated solution of ammonium sulphate, thus minimizing the amount of bilirubin absorbed by the proteins of the serum

The significance of this modification is emphasized by the figures presented by Barron (79) In those instances of jaundice where the diazo-reaction was biphasic, the determination of the blood bilirubin by the Thannhauser and Anderson method showed an increase of from 20 to 37 per cent over the values obtained by the original van den Bergh technique Where the reaction was direct the discrepancy was even more marked, the increase varying from 29 to 42 8 per cent

On reviewing the literature one finds that the normal values for circulating bilirubin vary within wide limits Thus, van den Bergh (80) found that normally the blood bilirubin varied between 0 1 and 0 3 mgm per cent, while Perkins (81) quotes 0 5 to 3 5 mgm per cent as normal Other authors quote figures somewhere between these two extremes In our own experience the values cited by Hasselhorst

(82) and by Barron (79) of 0 1 and 0 5 mgm per cent, although somewhat too low, more closely approximate the usual average in healthy humans

Physiologically certain daily variations in the blood bilirubin content occur   Thus, fasting increases the blood bilirubin and consequently the highest figures are obtained before breakfast   Much lower values are usually found several hours after meals

Pathologically, a hyperbilirubinemia will occur under three sets of circumstances

   1   Where the liver parenchyma is diffusely involved in some disease process as it is in catarrhal or arsphenamine jaundice

   2   Where obstruction to the excretory ducts of the liver is present

   3   Where excessive hemolysis of the red cells takes place

Unfortunately in those other pathological conditions such as cirrhosis or new growths of the liver, where the process is more or less localized in the sense that not all the parenchymal cells are disturbed, an increase in serum bilirubin not infrequently fails to occur   Of 100 instances of clinically well established cases of liver disease, which does not include the acute episodes mentioned above, fully one-half showed normal blood bilirubin values   The explanation undoubtedly resides in the fact that because of the tremendous reserve power of this organ, the excretion of this pigment was adequately cared for even in the presence of extensive although not universal parenchymal damage In the end stages of portal cirrhosis or even earlier in the so-called biliary cirrhosis, where extensive distortion of the continuity of the smaller bile channels has taken place, bilirubin begins to accumulate in the blood stream and manifests itself clinically   Until shortly before this stage is reached the quantitative estimation of blood bile pigments very often fails to reveal any decided increase   It is rather interesting that, although the reserve power of the liver in these cases is adequate for handling the amount of bilirubin which is normally made and brought to it for excretion, when an additional burden is thrown on the excretory function of the cells by artificially increasing the amount of bilirubin in the blood, evidence of impaired excretory ability is often revealed   This will be discussed in greater detail later

2 Qualitative van den Bergh reaction

The van den Bergh reaction is based essentially on Ehrlich's (83) discovery that a mixture of sulfanilic acid, hydrochloric acid, and sodium nitrite yielded a reddish violet color when added to solutions containing bilirubin   The chemistry of this reaction was subsequently elucidated by Prosher (84) who showed that bilirubin combines with the diazobenzolsulphochloride to form acetophenolazorubin   Recently, Kerpolla and Leikola (85) definitely proved that the color of the diazo-reaction was due partly to oxidation of the bilirubin and partly to the action of acid

Van den Bergh and Muller (86) were the first to point out that in certain types of jaundice, notably obstructive jaundice, the reddish violet color occurred promptly on the addition of the diazo reagent to blood serum   In contrast to this, the serum of patients with hemolytic jaundice required the addition of alcohol before a color reaction took place   Thus, the notion of "direct" and "indirect" reactions developed   Some three years later, Feigl and Querner (87) demonstrated still a third type of reaction   They noticed that in some cases of jaundice, on the addition of Ehrlich's reagent to the serum, the color reaction appeared at once but reached its maximum intensity some time later   This was spoken of as the "biphasic" reaction

The significance of these various color reactions cannot be overestimated   Through them we have a laboratory means of determining not only the degree of hepatic damage, but also the type of damage that exists in instances of jaundice   Correctly interpreted these reactions serve as useful guides in determining the extension or regression of the pathological process

The cause for the differences in color reaction produced by the sera of jaundiced patients is still a mooted and confused point   In view of the excellent discussion of this phase presented by Barron (79) in his review, we shall not discuss it in any great detail   Several points however bear emphasizing   Bilirubin which has passed through the epithelial cells of the liver, but is not excreted due to obstruction of the bile ducts yields a "direct" reaction when it is regurgitated into the blood stream   In contrast to this, bilirubin which has not yet passed through the liver cells, yields a delayed or "indirect" reaction   This

difference in the reaction of the pigment is in all probability not due to any inherent differences in the character of the bilirubin, but rather dependent upon the medium in which the pigment is contained Thus Barron (79) found that while a solution of pure bilirubin of the same pH as that of the blood yields a direct reaction, if it be added to normal plasma the reaction becomes indirect He attributes this to the absorption of the pigment by the serum proteins, which thus prevents it from reacting with the reagent promptly This also might reasonably explain the fact that while bile pigment which reacts immediately with Ehrlich's diazo reagent is excreted with great facility by the kidneys, the pigment yielding the indirect reaction is excreted with great difficulty in the urine Barron (79) further found that when substances which lower the surface tension of plasma are introduced before the bilirubin is added the reaction will remain "direct" It would seem that such substances are more readily absorbed by the proteins thus permitting the pigment to remain free in solution

Regardless of the chemical explanations that account for the variations in the van den Bergh reactions, the presence of these variations helps to determine the pathogenesis of the different types of jaundice Where the reaction is direct, one of two types of pathological change has occurred Either there is obstruction of the larger bile channels from within or without, or else extensive diffuse necrosis of the parenchymal cells has taken place The presence of such severe damage to the cells disrupts the continuity of the smaller bile canaliculi permitting the bilirubin to be regurgitated into the blood stream through the perivascular lymph spaces Such directly reacting bilirubin is excreted in the urine when the renal threshold is exceeded (2 to 3 mgm per cent) None is found in the stools

The pathological explanation for "indirect" reacting bilirubin resides in the fact that the polygonal cells are not capable of excreting into the bile channels all of the pigment which is brought to them Thus, in the early stages of toxic jaundice produced by arsphenamine, or in mild catarrhal jaundice where there is comparatively slight diffuse damage of the parenchymal cells these cells are incapable of adequately excreting all of the bilirubin which is normally brought to them and some is retained in the blood stream in its "bound" form

In cases of hemolytic jaundice, two factors probably operate   There is increased bilirubin formation and the existence of some impairment of the excretory power of the liver cells   In view of the tremendous reserve power of the liver (shown by McMaster and Rous (88), who found that 95 per cent of the excretory function of this organ may be removed in the dog without the appearance of jaundice), it is inconceivable that any degree of hemolysis compatible with life will produce enough bilirubin to embarrass the excretory function of normal, healthy liver cells   Rich (89) has pointed out that anoxemia produces definite pathological alterations of the liver cells around the efferent veins of the lobules which interfere with the function of these cells   In hemolytic anaemia as well as in pronounced anaemias from any cause such changes actually take place   Hence, in the former condition we have not only an increase in the amount of the bilirubin formed but also we find that the liver cells are sufficiently damaged to interfere with their ability to excrete this excessive pigment   The bilirubin thus retained yields an indirect reaction   Unlike the bile pigment in obstructive jaundice it is not excreted by the kidneys so that the urine is relatively free of bile, but large amounts of urobilin and urobilinogen are found   While normal liver cells are capable of reconverting into bilirubin the small amount of urobilinogen which is normally brought to them through the portal circulation, in the presence of diffuse parenchymal damage this task is less effectively performed

The biphasic reaction is probably due to the simultaneous presence of bound and free bilirubin in the blood serum   Pathologically it would indicate both some degree of obstruction of the bile canaliculi and some diffuse alteration of the parenchymal cells   The difference between the so-called "prompt" and "delayed" biphasic reaction is in all probability an expression of the degree of obstruction of the smaller bile channels

The various types of reacting sera and their conversion one into the other is best seen in a condition such as arsphenamine jaundice   Early in the development of arsphenamine jaundice where the pathological process is that of a mild although diffuse, cloudy swelling of the cells, the excretion of the bile pigment through these cells is interfered with and some of the bilirubin is retained in the blood stream   At this

stage the blood serum would yield an indirect reaction   As the lesion becomes more severe with necrosis of some cells, the continuity of the bile canaliculi adjacent to these cells is disrupted   Now we see that there is not only difficulty in the passage of the pigment through the parenchymal cells, but we find that pigment which has already passed through is blocked in some of the bile canaliculi, notably those adjacent to the most necrotic parenchymal cells   The blood serum now yields a "biphasic" reaction   The process may go on to the point where diffuse necrosis of the liver cells is present   The continuity of all the smaller intrahepatic bile channels is disrupted with general obstruction to the passage of bile   At this stage the "direct" reaction will manifest itself

When healing begins to take place the reaction will change from "direct" to "biphasic" to "indirect" and eventually it will become negative   It thus becomes evident that the various reactions indicate in a general quantitative way the extent of the pathological changes which are taking place

3 The icterus index

When we determine the icterus index we are determining the degree of "yellow" intensity of a given serum as compared to a standard solution of potassium dichromate (1 10,000)   Thus, if a sample of serum has an icterus index of 5, it means that the yellow color of this serum is 5 times as intense as that of the standard potassium dichromate The legitimacy of this procedure is based on the assumption that the yellow color of the blood serum is due mainly to bilirubin

The technique as originally described by Meulengracht (90) consists of diluting 1 0 cc of serum with 0 9 cc of normal sodium chloride solution until the color matches the standard (1 10,000 potassium dichromate)   The solutions are then compared in a colorimeter, the icterus index being determined by the following calculations

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times \text{dilution} = \text{icterus index}$$

Meulengracht (90) established 1 to 10 units as the normal indices Maue (91) and Bernheim (92) state that the normal icterus index lies between 4 and 6   Ernst and Forster (93) modified the technique by

precipitating the serum with two volumes of acetone and after filtration compared this solution with the potassium dichromate standard

The icterus index ostensibly serves the same purpose as that of a quantitative van den Bergh, a means of determining the degree of bilirubinemia   The advantage of the former over the latter is its simplicity   Its great disadvantage however, lies in the fact that while the diazo reaction is specific for bilirubin, the icterus index is a measure only of the degree of "yellowness" of the serum   The color of serum may be influenced by substances other than bilirubin   It is well known that a diet rich in vegetables increases the color intensity of serum   This increase is not due to added bilirubin but to lipochromes (carotin, lutein, etc)   Stoner (94), and Hess and Myers (96) report

TABLE 1

Comparison of icterus index values to serum bilirubin in normal instances

NUMBER OF OBSERVATIONS	VAN DEN BERGH REACTION	SERUM BILIRUBIN	ICTERUS INDEX, UNITS			PERCENTAGE OF CASES IN WHICH THE ICTERUS INDEX IS ABOVE THE EXPECTED NORMAL
			5-9	10-12	Above 12	
		mgm per cent				
25	Negative	Less than 0 5	20	2	3	20
28	Indirect trace	Less than 0 5	20	3	5	28 5
Total 53		Less than 0 5	40	5	8	24 26

* Average

instances of considerable carotinemia in diabetic patients   Corotinemia may produce a clinical picture indistinguishable from jaundice This was shown by Hernando (97)   White (98) in a study of 26 nondiabetic cases found that an increase in the color of the serum due to carotin could be represented by a mean icterus index of one   This figure is much lower than we would suspect from clinical observations if we assume that the disparity between the serum bilirubin and the icterus index, which is not infrequently obtained in perfectly normal individuals, is an expression of the presence of substances other than bilirubin in the serum   In table 1 are presented 53 instances in which the serum bilirubin and the icterus index determinations were done on the same sample of serum   In none of these instances did the serum

bilirubin exceed the normal value of 0 5 mgm per cent   Of this group, 13 or 24 2 per cent showed an icterus index of 10 or more while 15 per cent showed icterus index readings above 12   The series is perhaps too small to permit any definite conclusions but at least it suggests that a discrepancy between the two tests not infrequently exists in normal instances

In those cases in which the serum bilirubin is above normal, there is no way of predicting the icterus index value   In other words, there is no definite correlation ratio between the latter value and the serum bilirubin content   This is clearly shown in table 2   The icterus index is anywhere from 5 9 to 26 1 times as great as the corresponding bilirubin values   Elton (99), who found a similar disparity, attempts to explain it on the grounds that the intensity of the color of a solution

TABLE 2

Factor by which the icterus index exceeds the serum bilirubin values

NUMBER OF OBSERVATIONS	VAN DEN BERGH REACTION	SERUM BILIRUBIN VALUES LOWEST AND HIGHEST FIGURES	ICTERUS INDEX LOWEST AND HIGHEST FIGURES	ICTERUS INDEX / SERUM BILIRUBIN	AVERAGE
		mgm per cent			
16	Delayed biphasic	1 0– 4 0	16–47	8 0–23	13 8
20	Prompt biphasic	2 3–16 0	37–188	6 8–26 1	11 1
15	Direct	4 0–17 4	45–154	5 9–18 5	9 7

will depend on whether the particles yielding the color are in crystalloid soluble form or are suspended in the medium as colloids, equal amounts of the former yielding a more intense color than the latter This explanation is based on the assumption that bilirubin yielding the immediate direct reaction is a crystalloid, while that giving an indirect reaction with the diazo reagent is in the form of a suspended colloid That this explanation is not entirely true is evidenced by several facts If we refer to table 2 again we note that in those cases where the "direct" reaction was present, that is, where most of the bile pigment is in crystalloid form, the icterus index averaged 9 7 times as much as the serum bilirubin, in contrast to 13 8 where the reaction was "delayed biphasic" in type   In the latter a good proportion of the pigment is ostensibly in the suspended colloid state   Furthermore, the lack of conformity between the icterus index and the serum bilirubin is equally

pronounced within the individual groups   Thus, the disparity is as marked in the "direct" reacting group as it is in those cases yielding delayed reactions   One might expect from Elton's explanation that within a given group the variations in the $\dfrac{\text{icterus index}}{\text{serum bilirubin}}$ ratio would be less marked, but this is obviously not so

The notion too, that the difference between the various types of reacting bilirubin is dependent on its existence in the crystalloid or colloid state is not entirely confirmed (78).

The icterus index is a simple and valuable procedure if it is always borne in mind that with it we are expressing only a comparison in intensity of color, and hence can only generalize as to the degree of bilirubinemia   Where the icterus index value is normal, it is safe to assume that there is no increase in the bilirubin content of the blood stream.   Slight increases in the icterus index must be interpreted with great caution since they need not necessarily indicate a hyperbilirubinemia   Markedly increased icterus index values usually indicate a hyperbilirubinemia, but express only in a general way the degree to which the serum bilirubin values are elevated   The sensitivity of the icterus index can be considerably increased by first precipitating the serum with acetone using the method described by Ernst and Forster (93)   This eliminates most of the hemolysis and produces a clear colored serum which may more readily be compared with the standards

4   Urobilinogenuria as a test of liver function

The enterogenous origin of urobilinogen has been generally accepted since the work of Muller (21) on this subject   Ellman and McMaster (100) have presented abundant evidence to support the view that in the uninfected animal the intestinal tract is the only site of origin of urobilinogen   The bile pigment is acted upon by the intestinal bacteria, and is converted into urobilinogen   The major part of this pigment is excreted in the stool while the remainder is absorbed through the intestine and brought to the liver by the portal circulation Normally, the liver will reconvert most of the urobilinogen brought to it into bilirubin and the rest is excreted as the chromogen in the urine In the presence of liver disease the amount of unconverted urobilinogen

excreted in the urine is considerably increased   Wallace and Diamond (27) performed a series of experiments which tended to support this theory concerning the metabolism of urobilinogen

There are several exceptions to the rule that urobilinogen is formed in the intestine   Thus when infection of the biliary passages is present the bile pigment may be converted into urobilinogen by the organisms present in these passages   Recently Rabinowitch (101) reported an instance in which urobilinogen was excreted in a tremendously high concentration in the urine of a patient with a large twisted ovarian cyst which contained blood   Several hours after removal of the cysts the urinary excretion of urobilinogen returned to normal   The contents of the cyst, which was sterile were exceedingly rich in this pigment   This is an instance where not only was the site of the pigment formation outside the intestines but also where bacteria played no part as reducing agents

These instances show that urobilinogen can be formed outside of the intestinal tract under certain conditions, but such an occurrence is uncommon and for practical purposes it may be considered that the intestinal tract is the usual site of formation   It is only on that basis that we can explain the significance of an increase or an absence of urobilinogen in the urine in relation to liver function

The methods commonly employed to determine the presence of urobilinogen and urobilin are dependent on (a) fluorescence in the presence of zinc salts (b) spectroscopic absorption bands and (c) production of a red color by the addition of Ehrlich's aldehyde reagent Recently Scott (102) described a simple colorimetric method for the quantitative estimation of urobilinogen

The fluorescence test is used for urobilin only and has been rendered practical by Schlesinger (103)   He introduced the saturated alcoholic solution of zinc acetate, which in slightly alkaline solution gives a green fluorescence with urobilin   Wilbur and Addis (104) introduced a very practical quantitative spectroscopic method for estimating the combined urobilinogen and urobilin content of urine   The simplest and most satisfactory method for determining the presence of urobilinogen in the urine, however, is the procedure introduced by Wallace and Diamond (27) based on Ehrlich's aldehyde reactions   The reagent consists of 2 grams of paradimethylamidobenzaldehyde in 100 cc of

20 per cent hydrochloric acid solution   The quantitative test devised by these authors consists of making a series of dilutions of the urine carried to a point where no further reaction takes place   To 1 cc of urine are added 10, 20, 30, 40, 50, etc , cc of water   Ten cubic centimeters of each dilution are placed in test tubes and 1 cc of Ehrlich's reagent is added   The characteristic pink color may appear promptly or within 5 minutes and is best seen by looking through the mouth of the tube   The appearance of the color may be hastened by warming the tube gently in a hot water bath

Urobilinogen is normally present in the urine in traces, and rarely exceeds a 1 20 dilution   Urobilin is never present in freshly voided urine, but on exposure to sunlight the urobilinogen is converted into urobilin   The accuracy of the test for urobilinogen will therefore be determined to a considerable extent by the freshness of the urinary specimen   The amount of this chromogen excreted varies during the course of the day   Best results are obtained by performing the test on a 24-hour urine specimen which has been carefully collected under toluol and kept in the icebox until ready for testing   It is advisable in instances of suspected liver disease where the urobilinogen values are low, to perform urobilin tests because considerable quantities of urobilinogen may have been converted into this pigment

The value of urobilinogen determinations as an index of liver function has been and still is a much disputed point   Opinions vary from the rather enthusiastic report of Piersol and Rothman (105) to the derogatory comments of Robertson and his co-worker (112)   In 24 cases of clear cut liver disease the latter workers found 7 instances in which the urobilinogen was present in the urine in amounts exceeding a 1 20 dilution   Meyer (107) studied the liver function in 100 instances of diabetes employing both the bromsulphalein and urobilinogen tests Of these 100 cases the urobilinogen test was positive in 10 instances, while the dye showed abnormal results in 21 patients and doubtful in 3

In our own series, urobilinogen determinations were made on 43 definite cases of various types of liver disease   Nine of these patients showed abnormal excretions of the chromogen   The distribution of this group of cases is as follows

13 instances of well defined cirrhosis of the liver with 3 positive urobilinogen tests

7 cases of primary and metastatic carcinoma of the liver with no
    positive urobilinogen tests

3 instances of biliary cirrhosis of which 2 yielded abnormal results
    with the urobilinogen test

12 cases of catarrhal and arsphenamine jaundice of which 3 showed a
    high excretion of this chromogen

4 cases of acute yellow atrophy of the liver with one positive result

4 instances of miscellaneous liver diseases such as hemachromotosis,
    congenital syphilis of the liver, pernicious vomitting of pregnancy,
    and Banti's disease of which none yielded positive urobilinogen
    determinations

In comparing the respective merits of the urobilinogen test with the
bromsulphalein, levulose tolerance and galactose tolerance tests we

TABLE 3

*Comparative results obtained with the urobilinogen, bromsulphalein, levulose toler
ance and galactose tests in patients with hepatic disease*

TYPE OF TEST	TOTAL NUMBER	POSITIVE RESULTS	PERCENTAGE
Urobilinogen	23	5	21 7
Bromsulphalein	23	13	56 5
Urobilinogen	28	7	25 0
Levulose	28	14	50 0
Urobilinogen	22	6	27 3
Galactose	22	7	32 0

found that the former test was not nearly as sensitive an index of
liver function as either the bromsulphalein or the levulose tolerance
test, while it did yield as many positive results as the galactose tol-
erance test (table 3)

The results cited above are somewhat misleading particularly in
reference to the cases of catarrhal and arsphenamine jaundice   It
was pointed out by Meyer-Betz (107) in 1913 that urobilinuria is found
only at the beginning and at the end of the course of catarrhal jaun-
dice   Wallace and Diamond (27) confirmed this finding with reference
to urobilinogenuria   The explanation probably lies in the fact that
during the height of this disease the parenchymal damage is extensive
enough to distort the continuity of the bile canaliculi producing an
actual obstructive lesion so that no bile enters the larger bile ducts

At this stage the van den Bergh reaction will be direct and urobilinogen will be entirely absent from the urine   When the reparative process begins and the continuity of the bile channels is again established there will be an outpouring of bile into the gastro-intestinal tract with a marked increase in the urinary excretion of urobilinogen

Daily determinations of urobilinogen are not infrequently of aid in the differentiation between obstructive and non-obstructive jaundice In the former there is a total absence of this substance in the urine However, in those cases of biliary obstruction that are associated with a cholangitis, urobilinogen will appear in the urine even though no bile passes into the intestines   The organisms along the infected biliary passages will convert the bile into urobilinogen which will be carried by the blood stream to the kidneys and thence excreted

Increases in urobilinogen will also occur in instances where active hemolysis has taken place as in pernicious and hemolytic anemia, malaria, and blood stream infections   Here the increase is present by virtue of the excess amount of bile pigment which is excreted into the intestines, although no liver disease need actually be present

B EXCRETORY TESTS OF LIVER FUNCTION

In this group are included the bromsulphalein test, the excretion of intravenously injected bilirubin and the rose bengal test   Congo red, and indigo carmine although originally employed in investigating the presence of liver disease have fallen into disuse and need not concern us here

1 Bromsulphalein liver function test

Bromsulphalein has replaced phenoltetrachlorthalein as a test of liver function since the former substance is much less irritating, dissolves in water with greater ease and disappears less rapidly from the blood stream   Toxic manifestations and venous thrombosis, a comparatively frequent occurrence when phenoltetrachlorthalein is employed rarely occurs with the sulfonated dye

Method   As originally described by Rosenthal and White (108), the test consists of injecting the dye intravenously in a dosage of 2 mgm per kilogram of body weight   Samples of blood are collected from the other arm at the end of 5 minutes and again after 30 minutes   One

sample of the serum is alkalinized with 3 drops of 10 per cent NaOH to bring out any change in color that may be present because of the dye This is compared with a series of standards in a comparometer box Another sample of serum is placed in the comparometer box directly behind the standard tube to give it the general color background of the serum   Normally, from 20 to 50 per cent of the dye is present in the circulating blood stream after 5 minutes, while all of the dye has disappeared from the blood after 30 minutes   Subsequently, Carl Greene suggested that 5 mgm per kilogram of body weight be used And in our experience this increase in dosage of the bromsulphalein has increased considerably the effectiveness of this particular test as an index of liver function   This amount of dye may be used safely No undue reactions have been recorded by any observers who have employed this amount

In our laboratory we have discontinued the collection of the 5-minute specimen since the value of the information thus obtained has proved to be questionable   At the end of one-half hour we have never found more than a trace of the dye to be present in normal individuals Retention of a measurable quantity—10 per cent or more, we consider definitely abnormal and therefore indicative of liver damage

In employing the bromsulphalein test it must be borne in mind that the dye is excreted by the liver through the biliary passages and into the gastro-intestinal tract   Obstruction of the bile ducts will produce a prolonged retention of the dye in the blood stream   Consequently an abnormal result obtained in instances where there is an obstruction of the main duct due to the presence of a stone or of neoplasm, does not necessarily indicate liver dysfunction   Similarly in instances of diffuse destruction of the liver parenchyma, where the continuity of the bile ducts is broken as in acute yellow atrophy, in parenchymal necrosis in cirrhotic livers, and in severe catarrhal and arsphenamine jaundice, the results obtained with this test are misleading   The abnormal retention of the dye need not be an expression of the inability of the liver cells to excrete it, since the obstruction of the intrahepatic bile channels as a result of their lack of continuity will cause the retention of the dye in the blood stream   This test ought never to be employed therefore, in instances of jaundice where the van den Bergh reaction is either direct or biphasic

In analyzing the data which have accumulated in the literature relative to the bromsulphalein test, we have attempted to eliminate all instances where the evidence of liver disease was not conclusive, as well as those cases where the van den Bergh reaction indicated an obstructive lesion   The general results recorded in the literature, as well as those obtained in our laboratory indicate the usefulness of this test as an index of liver functions   The test is most apt to yield positive findings where liver damage is as diffuse and extensive as it is in portal cirrhosis, particularly with ascites, and in biliary cirrhosis, while in instances of malignancy of the liver either primary or metastatic the results are less satisfactory

O'Leary, Green and Rowntree (109) studied 67 cases of various types of liver disease associated with syphilis and found the bromsulphalein test to indicate impaired liver function in 54 instances or 80 per cent   These authors employed the dosage of 5 mgm per kilogram of body weight   Of these patients 22 had so-called syphilitic cirrhosis and all of them showed abnormal retention of the injected dye   Of 17 cases of gummatous hepatitis 10 yielded positive dye tests   In this group there was still a good deal of normally functioning liver tissue although the gummata were wide spread in the liver   In 20 selected instances of post-arsphenamine jaundice where the bilirubinemia was of slight degree, 15 cases showed an increased retention of the dye

Cornell (110) employing 2 mgm per kilogram of body weight, studied 51 cases of various types of liver disease and found that 26 or 50 per cent yielded positive results   Here too, most of the abnormal results were obtained in those instances where the lesions were diffuse and extensive

Foley (111), also employing the 2 mgm dosage, investigated 68 cases of definite liver disease and obtained evidence of liver dysfunction with this method in 70 per cent of his cases   In 31 instances of chronic passive congestion of the liver, as well as in 14 cases of portal cirrhosis with ascites, the dye test was uniformly positive   Of 10 cases of carcinomatous metastasis to the liver however, only one showed retention of the dye after 30 minutes   In 13 cases of mild arsphenamine jaundice 9 showed a definite retention of the bromsulphalein after one-half hour, although in 7 the degree of retention was

slight   In 19 of the 23 cases he compared the results obtained with the bromsulphalein with the galactose tolerance and urobilinogenuria tests and found that 15 of these 19 cases yielded positive results with the dye test while only 8 of the galactose tolerance tests and 5 of the urobilinogenuria were abnormal

Robertson, Swalm and Konzelmann (112) performed the bromsulphalein test on 23 cases of hepatic disease and in 19 obtained evidence of impaired function   These authors also find that the use of

TABLE 4

Analysis of 82 bromsulphalein tests

DIAGNOSIS	NUMBER OF CASES	NUMBER OF POSITIVE RESULTS	PERCENTAGE OF POSITIVE RESULTS
Cirrhosis of the liver with ascites	15	12	80
Cirrhosis of the liver without ascites	17	9	53
Malignancy of the liver 1° and 2°	13	6	46
Miscellaneous diseases of the liver	37	11	30 0

TABLE 5

Comparison of the bromsulphalein test with the levulose tolerance galactose tolerance and bilirubin excretion tests in instances of liver disease

TEST EMPLOYED	TOTAL NUMBER OF CASES	NUMBER OF POSITIVE RESULTS	PERCENTAGE
Bromsulphalein test	52	29	55 8
Levulose tolerance test	52	28	53 9
Bromsulphalein test	30	23	76 7
Galactose tolerance test	30	6	20
Bromsulphalein test	18	3	16 7
Bilirubin test	18	16	88 9

the 5 mgm dose yields much more satisfactory results than when 2 mgm per kilogram of body weight are employed

In our own laboratory we performed a total of 82 bromsulphalein liver function tests   In a good many instances the evidence of liver disease was confirmed either at operation or at necropsy   In the remaining cases the clinical presence of liver disease was indisputable   In 31 of these 83 instances, 2 mgm per kilogram of body weight of the dye were employed   Seven or 22 5 per cent only, showed abnormal

results   Of the 52 cases where 5 mgm per kilogram of the dye were employed 32 were positive, or 61 6 per cent   Reference to table 4 shows that the greatest incidence of positive results was obtained in cases of portal cirrhosis with ascites   In malignancy of the liver either primary or metastatic increased retention of the dye is considerably less   In the group classed as "miscellaneous" which included instances of Banti's disease, Pick's disease, gummata of the liver and mild arsphenamine and catarrhal jaundice, the number of positive results obtained with the dye test was smallest

The data presented in table 3 demonstrate that the bromsulphalein test is a more sensitive index of hepatic dysfunction than is the urobilinogenuria determination   In table 5 are compared the results obtained by the dye test, the levulose tolerance test, the galactose tolerance test, and the test dependent on the excretion of intravenously injected bilirubin   The comparative studies of the various tests were done on the same cases, that is, in one group of cases were compared the bromsulphalein and levulose tolerance tests, in another group the bromsulphalein and galactose tolerance tests while in a third group of cases the dye test and the bilirubin tests were performed   In this comparative study an equal number of positive results was obtained by the dye method and the levulose tolerance test   I might point out here that in several instances of this group, 2 mgm per kilogram of body weight of the dye were employed   This dosage undoubtedly lowers somewhat the percentage of positive results obtained by this method   The dye test however proved to be much more sensitive than the galactose tolerance but much less so than the bilirubin excretion test   In this latter group were included only mild although definite instances of hepatic disease

Concerning the bromsulphalein liver function test the following generalizations may be drawn   In about 55 to 65 per cent of liver disease this test, employing a dosage of 5 mgm per kilogram, will yield definite evidence of impaired hepatic function   The percentage of positive results is considerably higher in cases where the liver damage is widespread and extensive as it is in portal cirrhosis with ascites, in biliary cirrhosis, and in long standing cases of chronic passive congestion   Where we deal with malignancies of the liver either primary or metastatic, retention of the injected dye after one-half

hour occurs less frequently, while in isolated lesions of the liver, as in hepatic gumma or cyst, the incidence of positive results obtained with the dye method is low   This test is considerably more sensitive as an index of liver function than either the galactose tolerance test or the determination of urobilinogen in the urine and yields a somewhat greater proportion of positive results in liver disease than does the levulose tolerance test

There is only a very rough quantitative relationship between the degree of retention of the injected dye and the extent of liver damage Not infrequently one finds patients with extensive liver disease and comparatively slight retention of the dye   In any particular case, however, that is followed over an extended period of time with this test, the results will indicate whether the hepatic lesion is becoming more extensive or is regressing

In the absence of jaundice, particularly of the obstructive type definite retention of the dye after one-half hour is indicative of impaired liver function   A normal result however does not exclude the presence of hepatic disease

2   The excretion of intravenously injected bilirubin as a test of liver function

In 1927 Von Bergmann (113) and his associate, Ellbott (114) studied the excretion of intravenously injected bilirubin in a variety of hepatic disorders particularly cirrhosis, chronic passive congestion of the liver, cholecystitis and miscellaneous cases of jaundice   In 1931 Harrop and Barron (115) conducted similar studies with this method and obtained satisfactory results   Somewhat later Jankelson and Gorgil (116) reported a series of cases of liver disease where this test was employed   Recently Soffer (117) and Soffer and Paulson (118) published the results obtained by the use of this method in women during the latter half of pregnancy, and in instances of post-catarrhal jaundice

The test is one which measures the excretory function of the liver, but in contrast to the dye tests, a substance is employed for measuring this particular function which is normally manufactured in the body The excretion of the intravenously injected bilirubin is entirely through the bile   This was demonstrated by Tarchanoff (10) and confirmed

by Vossius (11)   Only in those instances were bile pigment circulating in the blood stream yields a direct van den Bergh reaction, does any excretion occur through the kidneys   Experimentally the bilirubin solution, when it is injected intravenously, is promptly absorbed by the proteins of the blood serum and gives an indirect reaction   Consequently no excretion in the urine takes place   Neither is the injected bilirubin phagocytosed by the reticulo-endothelial cells   Kanner (119) studied the reticulo-endothelial system in different types of jaundice and found that only in cases of completely obstructive jaundice does any storage of bilirubin occur within the kupfer cells   He never found evidence of bilirubin deposition in either the kupfer cells or in any other part of the reticulo-endothelial system in instances of partial obstructive and non-obstructive jaundice

In view of these experimental findings, and the peculiar nature of the testing substance it would appear, theoretically at least, that this test should be ideal for investigating the excretory phase of liver function   It must be remembered that the test cannot be employed in any instance where there is a hyperbilirubinemia, that is where the liver cannot adequately handle the amount of bilirubin normally circulating in the blood stream   No further information could be gained by increasing the amount of this pigment already in the blood

Method   The method employed in this clinic is the one described by Harrop and Barron (115) with some modifications introduced by Soffer (117)   A total amount of bilirubin equal to 1 mgm per kilogram of body weight is dissolved in 15 cc of a one-tenth molar solution of sodium carbonate which has been previously brought to the boiling point and then allowed to cool to 80°C   The bilirubin dissolves completely and a clear iodine-colored solution is obtained   A control sample of oxalated blood is collected in a dry syringe and with the needle in situ the bilirubin is then injected intravenously   Oxalated samples of blood are obtained from the other arm within 5 minutes and again 4 hours after the injection   The concentration of bilirubin in the plasma is determined by means of the Ernst and Forster (93) method   The plasma is precipitated by redistilled acetone which is used in different concentrations depending on the amount of bilirubin in the sample   Thus, with the control and with the sample taken after 4 hours, 2 cc of acetone is added to 2 cc of plasma, while with

1 cc of the plasma of the 5 minute specimen, 4 cc of acetone are used After the plasma and acetone mixtures are shaken the samples are centrifuged and filtered directly into a dry micro-colorimeter cup and compared with a standard solution of 1 6000 potassium dichromate The bilirubin content of the specimen taken 5 minutes after the injection minus the bilirubin content of the control sample is considered as 100 per cent of the injected pigment The percentage of bilirubin retained in the sample taken after 4 hours is then calculated, after previous subtraction of the bilirubin contained in the control The following formulae are employed to determine the amount of bilirubin in the various samples

Control and 4 hour specimens

$$0\ 329 \times 2\ (\text{dilution}) \times \frac{\text{reading of standard}}{\text{reading of unknown}}$$

5 minute specimen

$$0\ 329 \times 5\ (\text{dilution}) \times \frac{\text{reading of standard}}{\text{reading of unknown}}$$

Harrop and Barron (115) performed this test on 10 normal individuals and found no retention of the injected pigment after 4 hours In 8 cases of various types of liver disease these authors performed the bilirubin, bromsulphalein, and levulose tolerance tests The bilirubin test was positive in all instances, while only one result was abnormal with each of the other tests In 7 cases of chronic anemia where liver disease was suspected, the excretion of intravenously injected bilirubin showed the existence of impaired liver function in 6 instances, while both the bromsulphalein and levulose tolerance tests were entirely negative

Jankelson and Gargill (116) employing a somewhat different method, performed the test on 5 instances of hepatic cirrhosis and on 6 cases of malignancy of the liver All showed an abnormal retention of the pigment

Of the 100 tests performed in our clinic, 28 were done on perfectly normal individuals In 15 of these there was no retention of the in-

jected pigment after 4 hours, while in 11 there was a retention of from
1 to 3 per cent and in 2 from 5 to 6 per cent   We have established
therefore, a retention of from 5 to 6 per cent after 4 hours as the upper
limits of normal

In table 6 are presented the results obtained in 72 patients with well
defined although comparatively mild instances of hepatic pathology
In 86 1 per cent of these patients a retention of the injected bilirubin
considerably above normal was shown   In table 5 the comparative
results of the bromsulphalein and bilirubin tests are shown   While
the former yielded 16 7 per cent of positive results, with the latter

TABLE 6

Analysis of 72 cases in which the bilirubin excretion test was performed

TYPE OF HEPATIC DAMAGE	NUMBER OF CASES	NUMBER OF POSITIVE RESULTS
Cirrhosis of the liver	13	12
Malignancy of the liver	4	2
Miscellaneous liver diseases	19	18
Diffuse liver damage with jaundice—after the jaundice has subsided	20	16
Second half of pregnancy	16	14
Total number of cases	72	62
Percentage of positive results		86 1%

method abnormal hepatic function was demonstrated in 88 9 per cent
of the cases   In 9 instances the bilirubin and levulose tolerance tests
were compared, 8 of these cases presenting abnormal results with the
former method with only 3 yielding abnormal levulose tolerance
curves

The opinions of the several investigators who have worked with the
bilirubin test are uniform   This is by far the most delicate of any
single test that is used to detect impaired hepatic function   While
the other methods yield satisfactory results where liver damage is
severe and diffuse, they are unsatisfactory in mild instances of hepatic
disease in contrast to the bilirubin excretion test which will show a
high incidence of abnormal results in this type of case

3 The rose bengal test

The rose bengal test was originally introduced as a clinical method for determining hepatic function by Delprat, Epstein and Kerr (120) in 1924   It had been previously demonstrated by Delprat that the dye which is di-sodium-tetra-iodio-tetra-chlor-fluorescine was entirely eliminated from the blood stream by means of the hepatic parenchyma and that the rate of elimination was definitely influenced by liver injury

Method   The method, as it was originally described by these authors, was somewhat too complicated and cumbersome for clinical use   It has subsequently been simplified and the exact technique is described by Delprat and Stowe (121)   Briefly, the test is performed as follows

Five to 10 cc of 1 to 2 per cent solution of rose-bengal in saline is injected intravenously   The amount of rose bengal used is not affected either by the body weight, age of the patient or by the sex   Two minutes from the start of the injection an oxalated sample of blood is collected which is designated as the "standard sample" and which contains the maximum concentration of the injected dye   This specimen is considered as containing 100 per cent of the rose bengal   Exactly 6 minutes later, that is 8 minutes after the dye has been introduced intravenously, the "unknown" blood sample is withdrawn   The plasma is separated and cleared by precipitation of the proteins with 2 volumes of acetone   This is centrifuged and to the plasma thus obtained a drop of 10 per cent NaOH is added to clear hemolysis   The resultant dye solutions are read in a colorimeter   Normally 50 per cent or less of the injected dye should be present in the circulating blood stream after 8 minutes   In view of the photosensitizing effect of rose bengal on tissues it is advisable to keep the collected specimens in the dark until they are to be read   Similarly, patients should be warned to avoid bright sunlight for several hours after the performance of the test   The author has further attempted to interpret the degree of retention of the dye in terms of "total liver function" and has introduced the following for this purpose

$$200 \times \frac{200 \times Rs}{Ru} \quad \frac{\text{(colorimetric reading of the 2-minute specimen)}}{\text{(colorimetric reading of the 8-minute specimen)}}$$

Recently Althausen, Biskind and Kerr (122) employed a spectroscopic method in the rose bengal liver function test   This method ostensibly retains all the advantages of the colorimetric method, but permits the test to be carried out in the presence of jaundice, moderate hemolysis and in lipemia, which had heretofore interfered with readings with the colorimeter

An analysis of the literature (123, 124, 125, 126) in reference to this test leaves one with the impression that the results are essentially similar to those obtained with the other dye methods   Where liver damage is as extensive and diffuse as it is in portal cirrhosis with ascites, the number of abnormal results obtained is proportionately high, while in cases of malignancy of the liver and in conditions where hepatic damage is comparatively slight, there is a smaller percentage of abnormal results

Again, there are reported many cases in which the rose bengal test was performed in the presence of severe jaundice with a direct van den Bergh reaction   The results obtained in these instances must be discarded since any abnormal retention obtained need not necessarily be explained on the basis of failure on the part of the hepatic parenchymal cells in performing this particular function   Where biliary obstruction is present retention of the dye will occur whether in the presence or absence of actual parenchymal liver disease

C METABOLIC TESTS OF LIVER FUNCTION

The two carbohydrates which are most frequently used to detect disturbances in liver function are levulose and galactose   Glucose has occasionally been used for this purpose, but the influence of factors other than the liver on the metabolism of this sugar renders it unsatisfactory as a test

1 Levulose tolerance test

The physiological considerations underlying the utilization of levulose for determining hepatic function have already been discussed   However, it seems advisable to mention the fact here that theoretically, levulose as a substance for testing liver function is less perfect than galactose since the former may be utilized by muscle and is to a very slight extent influenced by insulin   Interestingly enough,

despite the theoretical perfection of galactose, examination of data presented in the literature and our own observations reveal it to be a much less sensitive index of liver function than levulose

In 1899 Sachs (57) demonstrated levulosuria in hepatectomized frogs   Two years later Strauss (50) suggested the clinical use of levulose as a test of hepatic function   He has observed that 90 per cent of his patients with liver disease showed a levulosuria while most of his patients without hepatic pathology failed to show this finding   The method that he employed was rather crude and subsequently proved to be unreliable   One hundred grams of levulose was administered orally and the presence of sugar in the urine one hour later was considered to be abnormal   About a decade later Shirokauer (127) suggested the utilization of the blood sugar curve after the oral administration of 100 grams of levulose   Spence and Brett (128) subsequently reduced the amount of the sugar given by mouth, on a weight basis, and later Tallerman (129) administered an arbitrary amount of 45 grams and found that the results were as accurate as those obtained when graded amounts were used   Tallerman attempted to establish normal values for this test   He concluded that a rise of blood sugar exceeding 30 mgm per cent from the fasting level or where the height of the blood sugar curve exceeded 135 mgm per cent was indicative of hepatic dysfunction   King (130) studied the levulose tolerance test on 10 normal individuals and on 53 patients with definite evidence of liver disease   The highest rise among his normals was 18 mgm per cent   Thirteen of his patients with hepatic disease had cirrhosis and showed a diminished tolerance for levulose   The remaining 40 cases yielded a lesser incidence of positive results   Jolliffe (131) conducted extensive studies with this sugar on 47 normal individuals   He performed a total of 81 tests   The amount of levulose administered was roughly determined by the weight of the patients   Thus, patients weighing between 110 and 165 pounds received 40 grams of levulose, while those over 165 pounds were given 50 grams   The highest individual blood sugar reading obtained was 121 mgm per cent   In 79 tests (97 per cent) the level reached was not over 115 mgm per cent   The maximum rise was 31 mgm per cent from a fasting level of 69 mgm per cent   Jolliffe concludes that the height of the rise is in proportion to the fasting level of blood sugar, conse-

quently it is important to consider the level of the fasting sugar before attempting to determine whether or not a particular levulose curve is abnormal   He further concludes that in any levulose tolerance test a blood sugar curve is considered abnormal when its height is more than 125 mgm per cent regardless of the level of the fasting blood sugar   Kimball (132) published an excellent report in which 480 levulose tests were performed, one hundred of these tests were done on patients who showed neither clinical nor laboratory evidence of liver disease   His findings on these hepatically normal patients agreed quite well with the results reported by Jolliffe (131)   In no instance was there an increase of 30 mgm per cent or more and in no instance was the blood sugar at the end of 2 hours more than 10 mgm per cent above the fasting level

The observations we have made bear out the findings reported by Jolliffe and by Kimball and accordingly we have adopted the following criteria as evidence of an abnormal levulose tolerance test

1   With a fasting blood sugar level of 80 to 100 mgm per cent an increase of 30 mgm per cent or more

2   With a fasting blood sugar level of 70 to 80 mgm per cent an increase of 35 mgm per cent or more

3   With a fasting blood sugar level of 60 to 70 mgm per cent an increase of 40 mgm per cent or more

4   Where the height of the blood sugar curve exceeds 130 mgm per cent regardless of the fasting sugar level (provided it is not above 115 mgm per cent) the curve is considered abnormal   Where the fasting blood sugar level is more than 130 mgm per cent, the possibility that the patient may be a diabetic enters and interpretation of the curve may then be misleading

5   Regardless of the height of the curve the failure of blood sugar after 2 hours to return to within 15 mgm per cent of the fasting level is considered abnormal

We found, too, that a definite relationship existed between the time of the curve at which the highest blood sugar level was reached and the extent of hepatic involvement   Thus, in 27 of 38 abnormal levulose tolerance curves, the maximum rise in blood sugar occurred ½ to 1 hour after the administration of levulose   In 7 instances the maximum increase was manifested after 1½ hours while in 4 the great increase oc-

curred at 2 hours   In the latter 11 instances where the highest point in the curve was reached after $1\frac{1}{2}$ to 2 hours the most extensive involvement of the liver showed clinically

It is rather difficult to determine the incidence of positive results obtained with this test in liver disease as reported in the literature, since the standards which are now considered abnormal varied considerably until the appearance of the results of the work of Tallerman about 10 years ago   Since then several excellent papers have appeared, the most noteworthy one of which is Kimball's (132)   Kimball reports results obtained on patients with frank liver disease both severe and mild, and on another group with diagnoses such as arthritis and asthma where the question of whether or not the liver is involved is a much disputed point   I have taken the liberty of discarding this latter group and considering only those patients with definite liver disease   There were in all 142 cases, 81 of these (or 57 per cent) yielded abnormal levulose curves   Here, too, the incidence of abnormal curves was higher in patients with severe hepatic damage Thus, in 69 of these 142 cases, which included cases of advanced cirrhosis of the liver, malignancy superimposed on cirrhosis, amebic hepatitis, etc , the percentage of positive results was somewhat higher (62 3 per cent) than the general figure quoted above, while of 73 instances of alcoholism with hepatitis, 52 per cent yielded abnormal curves   RaO (133) performed the levulose test on 37 cases of definite hepatic disease, 25 of which (67 5 per cent) yielded abnormal results Twenty-eight of these cases were instances of cirrhosis and 21 (75 per cent) of this group were positive

In our own clinic a total of 70 levulose tolerance tests were done on patients with definite liver disease   Thirty-eight or 54 3 per cent of these 70 gave abnormal levulose curves   This figure compares closely with the general figure obtained from Kimball's report   The analysis of this group of 70 cases is shown in table 7   It will be seen that the greatest incidence of positive results was obtained in patients with cirrhosis of the liver (78 5 per cent) particularly when associated with ascites

In tables 3 and 5 are shown the comparative percentages of positive results obtained in the same cases, with the urobilinogen and levulose tolerance tests and the bromsulphalein and levulose tests   The levu-

lose tolerance yielded a greater incidence of positive results tban the urobilinogenuria determinations (50 per cent in contrast to 25 per cent with urobilinogen determination) While the percentage of positive results was essentially the same as that yielded by the brom-sulphalein test (levulose, 53 9 per cent, bromsulphalein, 55 8 per cent), the latter figures are somewhat misleading, since included in the bromsulphalein series were some instances in which only 2 mgm per kilogram of the dye were employed With the large dosage of brom-sulphalein the incidence of positive results would be somewhat higher

The respective merits of levulose and galactose will be considered when the galactose tolerance test is discussed

Method for performing the levulose tolerance test In this clinic the following procedure is employed in performing the levulose tolerance

TABLE 7

Analysis of 70 levulose tolerance tests

DIAGNOSIS	NUMBER OF CASES	NUMBER OF POSITIVE RESULTS	PERCENTAGE OF POSITIVE RESULTS
Cirrhosis of the liver	28	22	78 5
Malignancy of the liver 1° and 2°	10	6	60 0
Jaundice due to diffuse liver disease	16	4	25 0
Miscellaneous cases of liver disease	16	6	37 5
Total number of cases	70	38	54 3

test, a fasting blood sugar is obtained early in the morning and directly afterwards the patient is given either 40 or 50 grams of levulose dis-solved in 250 cc of water (40 grams are employed where the patient weighs less than 140 pounds) Samples of oxalated blood are collected at half hour intervals after the administration of the levulose, for a period of 2 hours and the sugar values then determined It is im-portant to precipitate the blood promptly after it is collected since if it is permitted to stand for any length of time some consumption of sugar by the leucocytes in the blood occurs (134) During the period of the test neither food nor water is permitted the patient In per-forming the levulose tolerance test it is of utmost importance to employ pure levulose The presence of even small amounts of glucose in the levulose will produce a not inconsiderable elevation in the blood

sugar level   Impure levulose is also irritating to the gastro-intestinal tract occasionally producing nausea, vomiting and diarrhoea

2 The galactose tolerance test

The galactose tolerance test was originally introduced by Bauer (51) in 1906   The test was neglected for a good many years, and in this country Shay (64, 140) and his co-workers were chiefly responsible for reviving interest in it, although a good deal of work had previously been done with this test in Europe particularly by German and Austrian investigators

Method   The method employed is the one described by Shay, Schloss, and Rodes (140)   The test is preceded by a 12-hour fast and on the morning of the test the patient is given no breakfast   A fasting specimen of urine is obtained and tested for sugar, then the patient is given 40 grams of galactose dissolved in 250 to 500 cc of water During the period of the test, food must be witheld though water may be given ad lib   The patient is asked to void at hourly intervals for a period of 5 hours after the administration of the galactose and all the urine voided at these intervals is collected separately and labeled The individual specimens are tested for sugar and the positive samples are added together and the sugar determined quantitatively by the Benedict method   Excretion of more than 3 0 grams of sugar during the 5 hour period is considered abnormal

The test may also be employed in diabetics since according to the work of Shay, Schloss and Bell (64) utilization of galactose by the liver is independent of the condition of the pancreas   The urinary sugar in a patient with diabetes may be removed by rapid fermentation with a yeast suspension   According to Shay, Schloss and Rodes a complete destruction of dextrose in the urine is obtained while the loss of galactose does not exceed 10 per cent by this method   A weighed amount of fresh yeast is suspended in 5 to 10 parts of water, the suspension is centrifuged, the water decanted and the operation is repeated until the supernatant fluid is clear and contains no reducing substance as determined by Fehling's solution   A 10 per cent suspension of the yeast is then prepared and the urine and yeast suspensions are mixed in the proportion of 1 part of urine to 7 7 parts of yeast   The mixture is then incubated for 45 minutes and tested for

sugar   Whatever sugar is present represents the galactose excreted during the tolerance test

The chief field of usefulness of the galactose tolerance test is in the differentiation between obstructive and non-obstructive jaundice Wörner (135) up to 1919 had collected from the literature 165 cases of catarrhal jaundice in which this test had been performed   One hundred thirty-three or 80 5 per cent had shown a urinary output of galactose during the test period exceeding 3 0 grams   In 132 collected cases of jaundice due to stone or neoplasm, only 9 to 6 8 per cent gave readings above 3 0 grams   Weiss and Hollas (136) performed 41 galactose tolerance tests on 25 patients with liver disease   Twenty-nine of these tests were done in 16 patients with diffuse liver disease with jaundice (catarrhal and arsphenamine) and 80 per cent yielded abnormal results   The other 12 tests were performed on patients with miscellaneous hepatic pathology, only 2 of these were positive, and these two were on the same patient

Shay, Schloss and Rodes (140) studied the galactose tolerance in 17 cases of catarrhal jaundice and in 18 cases of obstructive jaundice All of the instances of catarrhal jaundice showed an excretion of more than 3 0 grams of galactose during a 5 hour period, while the sugar excretion in the cases of obstructive jaundice did not exceed 2 20 grams

Mancke (137) reported the results of 67 galactose tests performed on 32 cases with diffuse liver damage with jaundice, 24 cases of cirrhosis and 11 cases of cholecystitis with cholelithiasis   Twenty (62 5 per cent) of the jaundiced cases showed abnormal excretion of this sugar while 8 (33 3 per cent) of the cirrhotic cases yielded pathological results   Of the 11 cases of obstructive jaundice, two were abnormal

A very excellent paper was published by Banks, Sprague and Snell (138) in this country. They carefully investigated 127 instances of various types of liver disease by means of the galactose test   They performed 37 tests on 18 cases of intrahepatic jaundice (arsphenamine, cincophen and catarrhal)   Twenty-three of these (62 2 per cent) were positive. Of 16 tests on patients with portal and biliary cirrhosis only 3 (18 7 per cent) yielded abnormal figures   There were 69 instances of proved obstructive jaundice due to extrahepatic neoplasm

and common duct stones, without liver damage, and 22 or 33 per cent excreted more than 3 0 grams of galactose during the test period In 21 cases of liver disease without jaundice both the galactose and the bromsulphalein tests were performed   There were 15 positive instances with the dye while only 2 of the galactose tests were abnormal Further data concerning the value of this test was provided recently by Herman (139) and by RaO (133)   The former author studied 28 cases of cirrhosis of the liver with the galactose tolerance test   Only 7 or 25 per cent of these were positive   RaO compared both the levulose and galactose tolerance tests on 10 patients with definite evidence of liver disease   The former test yielded 6 positive results, while only 3 were obtained with the latter

TABLE 8

Analysis of 46 galactose tolerance tests

DIAGNOSIS	NUMBER OF CASES	NUMBER OF POSITIVE RESULTS	PERCENTAGE OF POSITIVE RESULTS
Cirrhosis of the liver	17	3	17 6
Malignancy of the liver 1° and 2°	6	0	0
Miscellaneous cases	5	0	0
Arsphenamine and catarrhal jaundice	18	8	44 4
Total number of cases	46	11	24

In our laboratory the galactose tolerance test was performed in 46 patients with a variety of liver diseases   The analysis of these data is given in table 8   Eleven of the 46 cases (24 per cent) excreted 3 0 grams or more of galactose during the test period   In table 5 are compared the results obtained in 30 instances of liver disease in which both the bromsulphalein and galactose tests were done   In this group the dye method proved to be considerably more sensitive as an index of liver function, since 76 7 per cent gave positive dye tests while only 20 per cent of the galactose tests could be interpreted as abnormal   The galactose test, however, proved to be somewhat more frequently positive than the urobilinogenuria determination in the 22 instances in which comparative tests were carried out (table 3)

The results obtained in the comparative studies with levulose and galactose in the same patients are interesting   They are presented in

table 9   It is seen that as a general test of liver function the study of the galactose tolerance is not as satisfactory as the information obtained from investigating the levulose tolerance   In patients with jaundice of either the catarrhal or arsphenamine type, or with jaundice resulting from acute parenchymal necrosis superimposed on a cirrhotic liver, the two tests are equally sensitive   It is rather surprising that we did not obtain a higher incidence of positive results with the galactose test in this group of jaundiced cases   The explanation may reside in the fact that in several of the cases the tests were performed towards the end of the acute hepatic inflammatory process

From a survey of the literature and our own experience we are justified in formulating the following conclusions concerning the

TABLE 9

Comparative studies on the levulose and galactose tolerance tests

TEST	TOTAL NUMBER OF CASES	NUMBER OF POSITIVE RESULTS	PERCENTAGE OF POSITIVE RESULTS	TOTAL NUMBER OF CASES OF DIFFUSE LIVER DAMAGE WITH JAUNDICE (ARSPH CATARRHAL, ACUTE NECROSIS IN CIRRHOTIC LIVERS)	NUMBER OF POSITIVE RESULTS	PERCENTAGE OF POSITIVE RESULTS
Galactose	38	9	24 0	25	10	40
Levulose	38	17	44 7	25	10	40

galactose tolerance test, in general liver disease, in the absence of jaundice, the test is one of the least sensitive of the many used in estimating hepatic function   Its greatest value lies in the differentiation in patients with jaundice, between the obstructive and non-obstructive types   In this it is definitely useful, although it must be borne in mind, that in a certain percentage of cases of obstructive jaundice positive galactose tests may be obtained   Under such circumstances the differentiation will depend on other data, notably, the clinical picture   Fortunately, this group of obstructive cases with positive galactose tests is relatively small   In the differentiation of jaundice the galactose tolerance test has definite advantages over the levulose test although the incidence of positive results is about the same with the two tests   In the first place, the former test is easier to perform and involves no particular hardship on the patient with the

exception of the prolonged period of fasting   But the elimination of venupunctures is a factor which most patients appreciate   Then again, the galactose test may be done in the presence of diabetes This group frequently presents jaundice as a cardinal sign of any one of a number of causes   The fact that neither the levulose nor any of the dye tests are satisfactory in these cases renders the galactose tolerance determination particularly valuable

D MISCELLANEOUS LIVER FUNCTION TESTS

The liver function tests to be considered in this group are tests which are not as frequently or as universally employed as are the tests previously mentioned   Some of them have been recently introduced into the literature, and only time and extensive experience with them will demonstrate their merit or lack of merit as laboratory procedures All of them have interesting physiological implications   There are a good many tests which we have failed to include   This discrimination has not been an arbitrary one   These latter tests in the course of time have demonstrated their lack of value and their retention in recent literature serves merely to confuse the problem of determining liver function   Tests dealing with the protein metabolism of the liver have at present no immediate application, but the brilliant work of Mann and his co-workers has helped to elucidate a field which may prove of tremendous value in the near future   It is for this reason that some of the work of these authors, and the clinical application of their results are considered here

1 Liver function tests based on the relationship of the liver to protein metabolism

Bollman, Mann, Magath (142) have shown that in completely dehepatectomized dogs there is complete cessation of urea formation The urea of the blood and tissues rapidly decreases as it is excreted in the urine, so that after several hours the amount of urea present in the blood, tissues and urine is minimal   Coincident with this drop in body urea there is an accumulation of amino acids in the blood, urine and tissues   Because of the fact that the amino acids are rapidly absorbed by the muscles where hepatic function is disturbed, the demonstration of an actual increase in amino acids in the blood or

urine in patients with liver disease is quite difficult except in the presence of the most extensive hepatic pathology   Recently, however, Mancke and Rohr (146) and Mancke (147) suggested the use of 50 grams of gelatin dissolved in 500 cc of water and administered orally as a test of liver function   In patients with catarrhal and arsphenamine jaundice and in patients with cirrhosis of the liver a considerable increase in the amino acid nitrogen ouput occurred in the urine

Apparently only the presence of a very small amount of normal liver tissue is necessary for the normal formation of urea   Thus Bollman and his co-workers (142) found that the most extensive reduction in the amount of hepatic tissue in dogs produces no decrease in urea formation   Wakeman and Morrell (143) conducted a series of nitrogenous studies in monkeys in which yellow fever had been experimentally produced   The outstanding pathological changes in this disease occur in the liver and it was only at the very terminal stages, a few hours before death, that a disturbance in the deaminizing function of the liver and a decrease of urea formation was noted   Clinically, a drop in blood urea is demonstrated only towards the end in patients with acute yellow atrophy   No change in the urea occurs in patients with the common chronic liver diseases   Rabinowitch (144) reported an instance of acute yellow atrophy in a young man of 28, in whom the cellular structure of the liver had almost entirely disappeared This case approached the experimental hepatectomy produced by Bollman, Mann, and Magath, and the blood chemistry findings were very similar to those reported by these authors   There was a complete absence of deaminizing power, a total absence of urea in the blood, and extreme hypoglycemia

Bollman, Mann, and Magath (145) further showed that in the dog at least, the liver was concerned with the destruction of uric acid   The complete removal of the liver in these animals produces a great increase in the uric acid content of the blood and tissues and the amount excreted in the urine is considerably increased   This increase in uric acid is manifested even in those animals where only small amounts of liver are removed and these authors claim that the increase in uric acid is roughly proportional to the amount of reduction of liver tissue These findings would suggest that the uric acid determinations might

be an excellent index of hepatic function, but in Wakeman and Morrell's (143) yellow fever monkeys and in Rabinowitch's (144) case of severe acute yellow atrophy no change in the uric acid content of the blood was noted   In Weiss' and Hollos' (136) series 17 uric acid determinations were made on 14 patients with catarrhal and arsphenamine jaundice and in no instance did an increase occur   And that is apparently the general experience of most clinicians   Changes in the uric acid content of the blood of patients with liver disease occur with such great infrequency that its utilization as a test is unsatisfactory The intravenous injection of uric acid as a test of liver function is fraught with a certain amount of danger since experimentally a uric acid nephritis is not infrequently produced

Other than the work of Mancke which shows promise but at present is technically difficult for practical clinical use, studies on protein metabolism cannot as yet be utilized in the early diagnosis of liver dysfunction   But this phase of hepatic physiology is still in its infancy and in time there may be evolved satisfactory methods for determining any alterations of this particular function

2 Methods depending on the detoxicating function of the liver

a Synthesis of hippuric acid   Quick (148) described a liver function test based on the conjugation of benzoic acid to form hippuric acid

Method   Five and nine-tenths grams of sodium benzoate are dissolved in 30 cc of water and administered 1 hour after a light breakfast of coffee and toast   The patient is given $\frac{1}{2}$ glass of water and is asked to void immediately after administration of the drug   This specimen is discarded and subsequent hourly specimens for four hours are collected, preserved with toluene and the hippuric acid content determined as follows   Each specimen is measured, transferred to a small beaker and acidified with concentrated hydrochloric acid until it is acid to congo red   The solution is stirred until the precipitation of hippuric acid is complete, and it is then permitted to stand for one hour   The precipitate is filtered, washed with cold water and then allowed to dry   The hippuric acid thus obtained may be weighed or it may be titrated with 2 N sodium hydroxide using phenolphthalin as an indicator   To obtain the total hippuric acid there must be added

to the amount thus obtained the quantity which remains in solution in the urine   This is usually in the proportion of 0 38 gram of hippuric acid in 100 cc of urine

Normally the output of benzoic acid as hippuric acid is from 3 to 3 5 grams during a 4-hour period   In patients with liver disease this figure is lower. Thus, Quick, studying patients with portal and syphilitic cirrhosis, found fairly constant outputs below this figure, although several low results were also reported by this author in patients with obstruction of the common duct due to neoplasm and, in several cases in patients with very doubtful evidence of liver disease   The series of cases reported by Quick is too small a one from which to draw any conclusions

Following the work of Bunge and Schmedberg (148) in the dog it has universally been assumed that the kidneys were concerned with the synthesis of hippuric acid   The evidence presented by Quick to prove that the liver is concerned with this synthesis in the human is not altogether convincing

b Cincophen oxidation test   This test was introduced by Lichtman (72) and is based on the supposed ability of the liver cells to oxidize cincophen   One of the intermediary products of this oxidation which is excreted in the urine is 2 (ortho-hydroxy)—phenyl-quinolin-4-carboxylic acid, or oxycincophen   In patients with liver disease the complete oxidation of cincophen is reduced and an increase in the intermediary product is found in the urine

Method   The test is performed as follows· A routine urine specimen is collected at 5 a m and the patient is then given 0 45 gram of cincophen by mouth   Total specimens of urine are obtained at 2-hour intervals until 10 p m and all the urine between 10 p m and 6 a m the following morning is saved as the final specimen   The usual diet, with only moderate amounts of fluid, is permitted during the test period   Each specimen of urine is filtered and 0 2 cc of the filtrate is added to concentrated hydrochloric acid to make a total volume of 5 cc , the mixture is next shaken and brought to a boil and a characteristic yellow color indicating the presence of oxycincophen should appear after the mixtures have been allowed to stand for 30 minutes   If the reaction does not develop then larger amounts of urine 0 4 to 0 8 cc are added to the acid   The amount of oxycincophen

present is determined by comparing the solution with permanent standard solutions in a comparometer box

The test was performed on 50 normal subjects and the amount of oxycincophen excreted in the urine over a 24-hour period varied from 30 to 100 mgm   Fifty-three instances of various types of liver disease were also investigated   There were 13 instances of cirrhosis of which 3 gave normal results, 4 cases of catarrhal jaundice in which the amount of oxycincophen excreted was within the upper limits of normal, 8 cases of so called toxic hepatitis all of which yielded abnormal excretion and 8 instances of carcinoma of the liver, one of which was primary   The amount of oxycincophen excreted by this group was well below 200 mgm   The remaining cases were those of obstruction of the common duct due to neoplasm and cases of cholecystitis with cholelithiasis   Many patients of this group showed an increase in the excretion of this intermediary product

It is obvious that the results obtained with this test are not startling In view of the uncertainty concerning the relation of the liver to this particular oxidative process and the theoretical danger of the administration of cincophen to patients with liver disease, its inclusion in the diagnostic armamentarium as a means of determining hepatic function ought to be reserved until more conclusive evidence of its specificity and value have been presented

3 The mercuric chloride reaction (Takata Ara test)

This test was originally designed by Takata (149) and by Takata and Ara (150) to differentiate between lobar and bronchopneumonia They found that when chest fluid from a patient with lobar pneumonia was added to a solution of sodium carbonate, mercuric chloride and acid fuchsin, a precipitation of mercuric oxide occurred   They believed that this precipitation was due to decreased stability of the serum proteins produced essentially by an increase in the globulin fraction   Somewhat later Staub (151) suggested that this reaction might be utilized in the diagnosis of cirrhosis of the liver since it had been demonstrated by several authors (152, 153) that parenchymal liver injury produced an increase in the globulin fraction of the serum proteins   Jezler (154) conducted extensive investigations with this test both on normals and on patients with a variety of hepatic and

other diseases   In 50 normal individuals the test was negative in every instance   In 220 instances of a variety of diseases in which the liver was not involved as in endocrine and metabolic disturbances, cerebrospinal syphilis, duodenal ulcer, pulmonary tuberculosis, etc , no precipitation reactions occurred   This author also studied the reactions in 155 instances of liver disease   In 43 cases of cirrhosis, the test was strongly positive in 38, weekly positive in 1 and negative in 3   In 3 instances of acute yellow atrophy, a marked precipitation reaction occurred   In 2 instances out of 21 cases of chronic alcoholism and in 2 out of 23 cases of chronic passive congestion of the liver, the test was positive   In the remaining instances of hepatic disease which included cases with catarrhal jaundice, syphilis of the liver, cholelithiasis, cholecystitis and cholangitis, the test was universally negative   Jezler further found that the test was as frequently positive when ascitic fluid from patients with cirrhosis was used, as it was with blood serum   The ascitic fluid due to other causes produced a negative reaction   The author determined the serum protein content, albumin fraction, globulin fraction and albumin—globulin ratio in 61 of these 155 cases of liver disease and in all instances he found that where the Takata reaction was positive there was a marked diminution in the albumin-globulin fraction with a considerable increase in globulin The total serum protein content plays no rôle in the production of this reaction   It is a phenomenon entirely dependent on an increase in the globulin content of the fluid   In patients with early cirrhosis the test is frequently negative   Apparently wide-spread and severe parenchymal changes must be present before positive precipitation occurs   The author concluded that the test is of great value in the diagnosis of hepatic cirrhosis and that the severity of the process may be gauged by the intensity of the precipitation   Crane (155), an American investigator working in Morawitz's laboratory, confirmed the results obtained by Jezler   In 21 instances of advanced portal cirrhosis, there were 20 positive reactions both on the blood serum and ascitic fluid   In 6 cases of carcinomatous metastasis to the liver the test was universally negative   In 18 cases of jaundice due to a variety of causes no precipitation occurred while in 2 cases of acute yellow atrophy the test yielded positive results

Unfortunately, no data have been collected as yet in the other con-

ditions where the albumin globulin ratio is disturbed as it is in nephrosis, or in the nephrotic types of nephritis with oedema But the evidence which has accumulated in the literature during the past 4 years would justify one's optimism concerning the value of this test, at least in differentiating advanced cirrhosis from other conditions which may produce a similar clinical picture

Method In each of a row of 8 small glass tubes is placed 1 0 cc of 0 9 per cent sodium chloride solution To the first tube is added 1 cc of the fluid to be examined This is mixed and 1 cc of the contents from this tube is removed and added to tube 2, then 1 0 cc is transferred from tube 2 to tube 3 and thus continued to tube 8 One cubic centimeter of the contents of this last tube is removed and discarded To each tube is then added 0 25 cc of 10 per cent sodium carbonate and 0 3 cc of the Takata reagent which consists of equal parts of 0 5 per cent mercuric chloride solution and 0 025 per cent aqueous Fuchsin Readings are made immediately after ½ hour and 24-hour periods Positive reaction are indicated by the appearance of a definite precipitate in 2 of the first 3 tubes and in any number of the following tubes Negative reactions may show no precipitate at all or only slight precipitation in the last 3 or 4 tubes

4 The initial insulin hyperglycemia test for liver dysfunction

In 1930 Burger (156, 157) described an elevation of blood sugar occurring in normal individuals 5 to 10 minutes after the administration of insulin This initial hyperglycemia was absent in patients with certain types of liver disease The mechanism of the test is apparently dependent on the ability of the intact liver to store glycogen which is liberated and converted into dextrose shortly after the administration of insulin The maximum increase in blood sugar usually occurs within 10 minutes after the insulin is injected and may be as high as 22 mgm per cent In patients with liver disease where the glycogen storage is disturbed, practically no initial increase in blood sugar occurs Unfortunately, as the author and many subsequent investigators have pointed out, the test is positive only in those instances associated with the most widespread and severe parenchymal damage such as occurs in acute yellow atrophy and in late portal cirrhosis In instances with mild and moderate hepatic damage the initial hyper-

glycemia is as marked as it is in normal individuals   The test therefore has a very limited field of usefulness

5 Macrocytosis as an indication of liver disease

The occurrence of macrocytosis or an actual macrocytic anemia in association with liver disease particularly cirrhosis has been reported in the literature   Wintrobe and Shumacker (158) have collected 57 cases of this type which have been reported up to 1927 and since then the occurrence of this anemia with liver disease has been recorded with even greater frequency

Schulten and Malamas (159) report a consistent occurrence of macrocytosis in all their cases of catarrhal jaundice and cirrhosis of the liver, while Fellinger and Klima (160) found a macrocytic anemia in 18 of 48 cases of cirrhosis, and Van Duyn (161) found 5 such instances among 28 cases of the latter disease   Wintrobe (162) conducted careful hematological studies in this hospital on 132 patients with various types of liver disease   In 25 of these cases (21 9 per cent) there was a definite macrocytic anemia   Of the 132 patients studied, 44 had cirrhosis of the liver and 15 of these presented a macrocytic anemia   There were 36 instances of primary and secondary hepatic malignancy of which 5 showed a definite hyperchromia   It is interesting as pointed out by Wintrobe that in all 5 instances there was also an associated cirrhosis   In 52 instances of miscellaneous liver diseases including catarrhal and arsphenamine jaundice, acute yellow atrophy, amyloid disease, etc , 10 showed macrocytosis

The macrocytic anemia in patients with liver disease is similar to pernicious anemia although there is generally less anisocytosis and poikilocytosis and the anemia is rarely as severe   The response to liver extract is, to a certain extent, dependent on the degree of the anemia present, and spontaneous remissions not infrequently occur That these cases do not represent the coincidental association of pernicious anemia and liver disease is suggested by the fact that achlorhydria was less common (40 per cent) in these cases than in those in which there was no macrocytosis (64 per cent)   The macrocytosis was observed only in cases of long standing and very widespread liver diseases

6 Hemoclastic crisis of Widal (proteopexic function of the liver)

In 1920 Widal, Abrami and Iancovesco (163) described a method which they believed tested the so-called proteopexic function of the liver   This test is based on the anaphylactic reaction which follows the introduction of a foreign protein into the body   Normally, the split products of protein digestion such as the peptones and proteoses are carried to the liver and there rendered innocuous   In the presence of liver disease this proteopexic function is impaired and the circulating split products produce the reaction described by Widal   This reaction which the authors termed the hemoclastic crisis is characterized by a leucopenia, fall in blood pressure, decrease in refractometric index of the serum and an increase in the coagulation time of the blood

The test as originally described by Widal and his co-workers (163) is performed as follows   Following a 5-hour fast a single control white cell count is made and immediately 200 cc of milk is administered orally   White cell counts are made at 20-minute intervals for a period of 2 hours   In the presence of liver disease a leucopenia develops usually within the first hour   In normal individuals a leucocytosis occurs   The authors of this test obtained a positive hemoclastic reaction in 38 out of 39 instances of hepatic disease

The value of the test as well as its theoretical basis are considerably in dispute   The question concerns itself as to whether the variation in the white counts obtained by Widal and his co-workers is not an expression of the normal diurnal variations in the number of leucocytes   Shaw (164) studied 7 patients with liver disease and 23 normal individuals, and concluded that the hemoclastic crisis is merely an expression of the phase of the normal curve at the time that the test was performed   Feinblatt (165, 166) performed this test on 80 normal persons and found a consistent leucocytosis, and while in 52 individuals with a variety of disease, 22 demonstrated a positive reaction   Although this author concludes that the reaction is indicative of faulty hepatic proteopexic function no evidence is presented to warrant the conclusions that the patients who presented a positive reaction had liver disease

Sabin, Cunningham, Doan and Kindwall (167) demonstrated that the leukocytes had a normal physiological rhythm regardless of digestion   At hourly intervals the leukocyte count reached a peak

which was followed by a depression in which the drop in the number of leukocytes occasionally reached 50 per cent of the preceding peak   It becomes obvious that if the test were performed at the time of the peak the subsequent drop would be erroneously interpreted as a positive reaction   Goodman and Connery (168) performed the Widal test on 17 patients with well defined liver disease   Two series of counts, a control and test series were performed on each patient and white counts were made at 15- to 20-minute intervals for a period of 2 hours The control series differed from the test series in that in the former instance the study was made on fasting patients, while 200 cc of milk was administered with the test series   The authors concluded from their studies that marked fluctuations in the total number of leucocytes occurred in both series and that there was no evidence that the ingestion of milk had any effect on the number of white cells in the peripheral circulation   These findings are in harmony with the observations reported by Martin (169) who studied the leucocyte variations in 6 normal persons and 3 patients with liver disease during a period of fasting and following the ingestion of a heavy meal including milk   The variations in leucocyte counts obtained after the meal were similar in degree to those obtained from the fasting subjects

It would appear from the reported observations that the relationship of the liver to the variations in leucocyte counts after food intake is a very doubtful one, since similar variations occur in fasting individuals

III DISCUSSION AND CONCLUSION

To appraise satisfactorily the functional status of the liver it is desirable to test as many functions of this organ as possible   A good deal of the present dissatisfaction with the results obtained with these tests is due to the tendency to rely solely on a particular test   There is no correlation between the type of pathological lesion present in the liver and the function which is disturbed   Nor is there any definite index, clinically, as to which function is disturbed first   This is well brought out by a comparison of the experimental studies of Mann and his co-workers with general clinical experience   In partially hepatectomized dogs they found that the first function to be impaired is the ability to destroy uric acid   Clinically, on the other hand, no change in the blood uric acid usually occurs except as a terminal

phenomenon in the presence of the most extensive hepatic damage Liver function tests have not reached the point of perfection where the nature of the test can indicate the type of change in the organ

In testing multiple functions of the liver one positive test is as significant an index of the presence of damage as would be the case if all the tests were abnormal There is, however, a rough proportionality between the extent of the injury and the number of positive results obtained Generally speaking, where the liver is more extensively damaged more functions are disturbed This should be regarded as a very general statement All clinicians can recall many cases of advanced portal cirrhosis where few if any tests were positive But here we are confronted with a problem that involves reparative efforts on the part of nature Regenerated areas of parenchymal tissue are as capable of performing the necessary function as are perfectly normal cells Hyperbilirubinemia, for example, very frequently does not occur in portal cirrhosis until the very end stages of the disease are reached Concerning any one particular liver function test, it is an index of the degree of liver damage or progression or regression of the lesion only when performed repeatedly on the same patient Thus, a dye retention of 60 per cent let us say, does not necessarily indicate a greater degree of liver injury than a 20 per cent retention in another patient, but an increase in the dye retained with repeated tests on the same individual indicates an increase in the degree of hepatic pathology

It is of utmost importance to the worker performing liver tests to recognize when these tests should not be employed There is no point in testing with dyes in the presence of a hyperbilirubinemia with a direct or biphasic van den Bergh reaction Since the dye is normally excreted by the liver into the intestines, the presence of an obstruction of either the large bile ducts or the intrahepatic canaliculi will produce retention of the dye irrespective of the fact that the kupfer and parenchymal cells may very well be able to excrete it The literature unfortunately is replete with reports of results obtained with dyes under such circumstances results which must be discarded as valueless Similarly the bilirubin excretion test can yield no information of any value when performed in the presence of a hyperbilirubinemia however slight Obviously, if the liver cannot handle the

amount of bile pigment which is normally brought to it, the further injection of bilirubin will yield no additional information

The carbohydrate tests are less limited in their field of usefulness The galactose test may be performed under all circumstances   In the presence of diabetes it is merely necessary to ferment out the glucose in the urine   The levulose tolerance test yields confusing results in the diabetic and although the influence of insulin on levulose is reported as minimal this test nevertheless should not be employed in the presence of the disease

It is rather difficult to appraise the merits of the various tests, but from examination of the literature and from our own experience the following conclusions are justified

Van den Bergh reaction   As a general test of hepatic function the quantitative van den Bergh reaction is inadequate, one sees too many instances of liver disease in which there is no increase in the amount of circulating bilirubin   Its greatest field of usefulness is in instances of jaundice   The quantitative van den Bergh is of course an excellent index of an increase or decrease in the intensity of jaundice   The qualitative reaction is of tremendous help in determining the progress of these patients   Its value in differentiating between obstructive and non-obstructive juandice is minimal   Patients with catarrhal or arsphenamine jaundice will frequently show a direct van den Bergh reaction in certain stages of the disease   But in these very patients repeated qualitative van den Bergh tests indicate the progress of the hepatic lesion   In the early stages of the disease the van den Bergh reaction is indirect and as the disease progresses the reaction becomes in turn biphasic and finally direct   Improvement is heralded by a reversal of the reaction and such changes usually occur even before the patient shows any clinical signs of betterment and before any decrease in the bilirubinemia is manifested   The differentiation between hemolytic and non-hemolytic jaundice by means of this reaction is unsatisfactory   Patients with a variety of types of liver disease may show indirect reactions in the absence of hemolysis, while less commonly, patients with hemolytic anemias will show biphasic reactions   The explanation of the results in this latter group is probably based on the liver cell damage which occurs as a result of the anoxemia due to the severe anemia

Icterus index The icterus index determinations must be interpreted with caution A normal icterus index definitely excludes hyperbilirubinemia, while a very high icterus index almost always means an increase in the bile pigment in the blood It is in instances where the icterus index is only moderately elevated that the results are frequently inaccurate The reason is that with this test we are merely measuring the depth of yellow color of a particular serum, which may be considerably influenced by the amount of hemolysis present This factor is eliminated to a great extent by the use of acetone in various proportions as suggested by Ernst and Forster The existence of lipochrome pigments in the serum may also cause an elevation of the icterus index in the presence of a normal bilirubinemia

There is no mathematical relation between the icterus index and the amount of blood bilirubin so that the former yields only very general information It is our feeling that it is worth while expending the little extra effort required to do the quantitative van den Bergh test in preference to the icterus index

Urobilinogen and urobilin determinations in the urine In our own experience these tests have proved to be of very little value in the general diagnosis of liver dysfunction In most instances of liver disease the results obtained were perfectly normal It is of some help in the differentiation between obstructive and non-obstructive jaundice The total absence of urobilinogen in the urine would suggest the former But here again it must be remembered that in certain stages of toxic and infectious hepatitis, obstruction due to changes in the small bile canaliculi occurs It is for this reason that urobilinogenuria is usually found only during the beginning and at the end stages of catarrhal and arsphenamine jaundice It must also be remembered that *in vivo* hemolysis of red cells may be produced by any number of causes, and infection of the biliary passages will produce a hyper-urobilinogenuria even in the absence of actual liver parenchymal damage

Excretory tests for liver function The results obtained with the bromsulphalein and the rose-bengal tests approximate each other The former test is somewhat more simple to perform Best results are obtained with bromsulphalein in a dosage of 5 mgm per kilogram of body weight A high incidence of positive results are found in cases

of cirrhosis particularly when associated with ascites   Abnormal
tests are much less frequently found early in cirrhosis and in metas-
tatic and isolated lesions of the liver

The most satisfactory, perhaps, of the excretory tests of liver func-
tion is the bilirubin excretion test   Abnormal retention of the injected
pigment is almost uniformly demonstrated in patients with cirrhosis
regardless of the stage   A greater incidence of positive results is ob-
tained by this method in demonstrating hepatic dysfunction in early
cases of liver disease than by any other method   As with most other
tests the bilirubin excretion test is usually negative where isolated
gummata or metastatic nodules are present   But the amount of
hepatic damage which must exist before the test is positive is con-
siderably less than with the other methods described

Carbohydrate tolerance test   The levulose tolerance test has proved
to be not quite as sensitive as the dye test as an index of liver function,
although more sensitive than either the urobilinogen or galactose
determinations   Disease of the liver must be widespread and mod-
erately severe before an abnormal response to levulose is manifested
Here too, the greatest incidence of positive results is obtained with
cases of cirrhosis with ascites, although even in this group negative
results are not infrequently encountered   The great advantage of the
levulose test lies in the fact that it may be used in the presence of
jaundice, obstructive or otherwise, to determine the existence of
hepatic dysfunction   The galactose tolerance test has proved to be
quite valueless in the diagnosis of liver disease in the absence of
jaundice   Its great field of usefulness lies in the differentiation be-
tween obstructive (as due to a stone or neoplasm) and non-obstructive
icterus   The literature is uniformly agreed on its value as an aid in
this differentiation   In this group of cases the levulose tolerance test
is as frequently positive but the simplicity of the galactose test renders
the latter the method of choice

Concerning the other liver function tests little need be said   At
present there is no valid reason for routinizing the detoxicating tests
for determining liver function   The insulin hyperglycemia reaction
has only a very limited field of usefulness   The method consisting of
injecting gelatin and of then noting the amount of amino acid nitrogen
excreted in the urine shows decided promise but more extensive studies

are required before any definite conclusions can be reached   Essentially the same is true for the Takata-Ara reaction   The ability to differentiate between hepatic cirrhosis and other types of liver disease and other causes of ascites will be of considerable help to the clinician, but time and experience will have to determine whether the enthusiasm manifested by its propagators is justified

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THE PATHOGENESIS OF CONGESTIVE HEART FAILURE

TINSLEY R. HARRISON

From the Department of Medicine, Vanderbilt University, Nashville, Tennessee

CONTENTS

I DEFINITIONS

The term "congestive heart failure," as used in this review, denotes passive engorgement occurring as the result of cardiac disease, whether appearing in the pulmonary vascular bed, the systemic circuit, or in both of these areas   The arbitrary restriction of this phrase to instances of systemic engorgement is unjustifiable, for congestion of the lungs, when due to cardiac disease, is obviously a manifestation of congestive heart failure   Not all heart failure is of the congestive type, and we are not concerned with the pathogenesis of acute cardiac collapse, which produces a different clinical picture and depends on different functional disturbances

The phrases "right-sided heart failure" and "left-sided heart failure" are employed to designate systemic and pulmonary engorgement, respectively   We are not concerned at the moment with the question of whether these terms should be used—this problem is discussed in detail throughout the review—but only with the fact that when these phrases are used they refer to the conditions mentioned

II THE COURSE OF HEART FAILURE

A *The stages of heart disease*   Regardless of the initial cause the majority of patients with disorders of the heart pass progressively through a number of stages, and although these merge gradually into each other they may be considered separately for the sake of convenience

1 *Potential cardiac disease*   This term refers to patients who lack subjective or objective phenomena of cardiac disease but who have some disorder such as hypertension or rheumatic fever which may lead to its development

2 *Asymptomatic cardiac disease*   This phrase designates the condition of individuals who have definite objective signs—such as cardiac enlargement or diastolic murmurs—of organic cardiac disease, but who are able to lead a normal life without symptoms referable to the heart   Asymptomatic cardiac disease is most commonly encountered in young patients with disorders of rheumatic or of congenital origin

3 *Diminished cardiac reserve*   This term refers to patients who are free of symptoms at rest but who suffer from dyspnea on the per-

formance of muscular exertion of a degree which could previously be performed without discomfort

4 *Failure of the left side of the heart*   This phrase denotes congestion of the lungs, which is manifested clinically by dyspnea at rest, decrease in vital capacity, rales at the lung bases, and cough

5 *Failure of the right side of the heart*   This term refers to the phenomena of systemic congestion, i e, edema, venous distention, enlargement of the liver, hydrothorax, ascites, albuminuria and cyanosis

6 *Cardiac cachexia*   This phrase designates a clinical syndrome characterized by asthenia, anorexia, loss of weight and anemia as the result of long-sustained congestive heart failure   Unusual susceptibility to infections is also a characteristic feature

B *The precipitating causes of heart failure*   In the majority of instances persons with cardiac disease pass progressively through the stages which have been mentioned, the underlying cause of the disorder being, with the notable exception of hyperthyroidism and profound anemia, relatively unresponsive to therapy   The progression from the earlier stages to the later and more serious phases of the malady is often precipitated by some added factor   The importance of such precipitating causes, which has recently been emphasized by Burwell (1935) and by Harrison (1929), has not been generally recognized   These agents are not ordinarily causes of cardiac *disease*, but since they are important causes of heart *failure*, and further, since they can be avoided and treated with some success, they are of no little practical importance

1 *Infections*, particularly of the respiratory tract, are by and large the most important of the several precipitating causes of heart failure The harmful effects of infections are dependent on (*a*) increased cardiac work as the result of the rise in metabolism produced by fever, (*b*) tachycardia, (*c*) direct injury to the myocardium, (*d*) cough, in many instances

2 *Exertion*, which was formerly considered the most important precipitating factor, is, as has been emphasized by Lewis (1933), of less importance than infection   Nevertheless, excessive exertion precipitates congestive phenomena in a fairly large group of persons with previously well tolerated cardiac disorders

3 *Cough* is much more important than has been generally recognized   It constitutes a form of severe exertion and is often associated with respiratory infection

4 *Pregnancy* is of especial importance in young women with rheumatic heart disease, as was clearly shown by Sir James Mackenzie (1921)

5 *Obesity* is a frequent and often preventable cause of congestive failure in persons already suffering from chronic cardiac disease

6 *Anemia* may of itself, when of great severity and long duration, cause congestive failure, but ordinarily it is simply an added factor in persons whose original cardiac disorder is due to other causes.

7 *Tachycardia* is an important element in the deleterious effects exerted by most of the other precipitating factors   However, rapid beating alone may precipitate heart failure, as is illustrated by certain cases of paroxysmal tachycardia   The relation of the heart rate to congestive heart failure is discussed in more detail in Section VII

8 *Changes in rhythm* may exert a deleterious effect either when they are associated with tachycardia or when they produce a pulse deficit.

9 *Emotional disturbances and prolonged mental strain* are rather rare causes of congestive failure but in some patients they appear to play a rôle   The demonstration by Grollman (1932) that fear, anger, etc , may increase the cardiac output would seem to constitute a reasonable explanation for the effect of psychic disturbances, which in addition may add to the load on the heart by raising the blood pressure

The effect of these various precipitating agents is to cause the patient with cardiac disease to pass from his present stage into the next more severe phase in the malady   From a practical point of view the prevention and treatment of these several precipitating causes of heart failure constitute perhaps the most important of all therapeutic considerations, particularly in persons suffering from cardiac disease in its earliest stages

III THEORIES OF THE MECHANISM OF HEART FAILURE

One hundred years ago James Hope (1842) taught that the fundamental functional change in persons with congestive heart failure was dilatation of the cavities of the heart and that the various clinical manifestations of this syndrome were dependent upon engorgement

ın the several vascular beds as the result of back pressure from the dilated cardıac chambers   He stated

"As an obstacle to the cırculatıon operates on the heart ın a retrograde dırectıon, the cavıty sıtuated ımmedıately behınd ıt ıs the first to suffer from ıts ınfluence   So long as the left ventrıcle ıs capable of propellıng ıts contents, the correspondıng aurıcle, beıng protected by ıts valve, remaıns secure   But when the dıstendıng pressure of the blood preponderates over the power of the ventrıcle, ıts contents, from not beıng duly expelled, constıtute an obstacle to the transmıssıon of the aurıcular blood   Hence, the aurıcle becomes overdıstended, and the obstructıon may be propagated backwards through the lungs to the rıght sıde of the heart, and there occa-sıon the same serıes of phenomena "

Hope's ıdea of backward faılure was generally accepted, and some of hıs enthusıastıc followers even went so far as to claım that faılure of one of the sıdes of the heart was always accompanıed by regurgıtatıon through the correspondıng aurıculoventrıcular orıfice   (It ıs ım-portant to note that Hope made no such statement   The ıdentıfica-tıon of the back-pressure ıdea wıth mıtral and trıcuspıd ınsufficıency has been a source of much unnecessary confusıon, as wıll be poınted out later)   A note of warnıng agaınst such overemphasıs of the functıonal ımportance of the heart valves was sounded by Wıllıam Stokes (1854), who wrote

"Prolonged and careful examınatıons are made to determıne whether the dısease exısts at the left or rıght sıde of the heart, whether ıt be a lesıon of the mıtral, trıcuspıd, or the semılunar valves, a contractıon or dılatatıon, an ossıficatıon, a permanent patency, or a warty excrescence   Now, though ın some, we mıght say ın many cases, these questıons may be resolved wıth consıderable accuracy, ıt ıs also true that ın a large number theır determına-tıon ıs of comparatıvely trıflıng ımportance, and the two great practıcal poınts to be attended are, first, whether the murmurs really proceed from an organıc cause, and next, what ıs the vıtal and physıcal condıtıon of the muscular portıons of the heart, for ıt ıs upon these poınts that prognosıs and treatment must entırely depend   It was long ago observed by Laennec that vulvular dıseases had but lıttle ınfluence on health when the muscular condıtıon of the heart remaıned sound, and every day's experıence confirms thıs observatıon "

In spite of Stoke's teachings the emphasis on valvular lesions persisted for half a century until Sir James Mackenzie again stressed the importance of the condition of the heart muscle   Mackenzie went further and discarded the back-pressure theory *in toto*, and substituted the forward-failure hypothesis (1921–1925)   According to this conception the clinical manifestations of congestive heart failure are due to an inadequate blood supply to the tissues as a result of diminution in the amount of blood pumped by the heart

These two ideas still have their proponents and opponents   The backward-failure conception is advocated by most pathologists and by most of the continental European clinicians   In Great Britain and America the forward-failure theory is generally accepted by clinicians and the idea of back-pressure has been discarded   Sir Thomas Lewis (1933), for instance, has recently written

"Breathlessness is to be ascribed to a deficiency in the flow of aerated blood to the head and neck, at first the deficiency is confined to those exercises in which normally the cardiac output is much above the resting value, at last there is a deficiency in the physiological quantity of aerated blood expelled by the heart while the body is at rest "

The same author expresses his idea of the back-pressure theory as follows

"In the old theory of back pressure the pressure was supposed to rise in the right ventricle before it rose in the veins and the tricuspid valve was pictured as one of the last lines of defense   Incompetence of this valve was regarded as the signal for engorgement of the veins, and so tricuspid incompetence came to be used almost as an equivalent for venous engorgement   Tricuspid incompetence forms an instructive example of an old-time clinical philosophy   An intangible valvular defect, draped with complex but unproved hypothesis, has formed a screen, tending to conceal the essential   The essential is not tricuspid incompetence, but general venous congestion, and the precise information that is required for practical purposes is obtained, not from the precordium, but from the veins themselves, for in this system lie the earliest, as well as the late signs of congestive failure   The veins provide direct signs, and those thoroughly familiar with them use neither the tricuspid murmur nor the theory that goes with it "

Before attempting a decision as to the relative merits of these two opposing conceptions of the mechanism of heart failure we shall consider the evidence upon which they rest

IV THE FORWARD-FAILURE HYPOTHESIS

The idea that the clinical manifestations of congestive heart failure are dependent on an inadequate tissue blood supply carries with it certain definite implications which are as follows

1 The output of the heart is subnormal, either actually or in proportion to the metabolic needs, in all cases

2 A quantitative parallelism must exist between the severity of the symptoms and the degree of diminution in the output

3 Beneficial therapeutic measures necessarily increase the cardiac output

4 Procedures which decrease the amount of blood pumped by the heart are necessarily harmful

5 The heart fails as a whole

6 Dyspnea, edema and the other important clinical manifestations of congestive heart failure are essentially and primarily dependent on decrease in blood flow to the tissues

7 Experimental diminution in the cardiac output in animals should produce a clinical picture similar to that seen in patients with congestive heart failure, when due allowance is made for the difference between acute and chronic conditions

We shall now consider the evidence bearing on these several propositions

A *The cardiac output in relation to congestive heart failure* Medical literature contains a number of reports dealing with the amount of blood pumped by the heart in persons with cardiac disease   These investigations may be divided into two general groups, according to the methods which have been employed to measure the output of the heart   We may consider briefly the results obtained by the older methods

In *patients with valvular lesions but without congestive failure* normal values for the cardiac output have been reported by Plesch (1909), Means and Newburgh (1915), Eppinger, Kisch and Schwarz (1927), Mobitz (1926)

and Smith, Walker and Alt (1930)   Subnormal values for the cardiac output were observed by Lundsgaard (1916), Meakins, Dautrebande and Fetter (1923), Meakins and Davies (1925), and Henderson and Haggard (1925)   Several authors [Plesch, (1909)] [Eppinger, von Papp and Schwarz (1924)] [Eppinger, Kisch and Schwarz (1927)] have reported certain cases with an increase in the cardiac output per minute

Similarly inconstant results have been found in patients with *congenital lesions*   Plesch reported high values, Petersen, Cristoffersen and Lindhard (1921) a low result   Weiss and Lowbeer (1924) calculated the amount of blood pumped by each ventricle in a patient with pulmonic stenosis and a septal defect   In their subject the output of the right ventricle was greater and that of the left ventricle was less than normal

Persons with *hypertension* but *without congestive failure* have been found to have low values for the cardiac output by Lauter and Baumann (1928) and by Lauter (1929)   On the other hand normal values were observed by Burwell and Smith (1929), by Weiss and Ellis (1930), and by Kroetz (1930), while Hayasaka (1927) and Ernst and Weiss (1929) reported increase in the output

Auricular fibrillation was found to be associated with subnormal cardiac output by Lundsgaard (1916), Henderson and Haggard (1925), Smith, Walker and Alt (1930) and Kerkhof and Baumann (1933)   These findings were confirmed in dogs by Stewart and Gilchrist (1928), using the direct Fick method   The patient studied by Davies, Meakins and Sands (1924) had a high cardiac output, but this subject, whose arrhythmia was due to thyrotoxicosis, cannot be regarded as comparable to the patients studied by the other authors

Meakins and Davies (1925) found subnormal cardiac outputs in each of two patients with *auricular flutter*

Complete heart block was associated with normal minute volume of the heart in the cases of Lundsgaard [1916 (2)], and of Smith, Walker and Alt (1930), but in Lauter's case (1930), this function was considerably diminished

Congestive heart failure was accompanied by subnormal cardiac output in six of the seven subjects studied by Lundsgaard [1916 (1)], in each of the three patients reported by Meakins and Davies (1925), and in Dautrebande's case (1928)   Stewart and Cohn (1932) found abnormally low cardiac outputs which increased as clinical improvement occurred   On the other hand the cardiac output was within the normal range in ten of thirteen patients studied by Mobitz (1926), and somewhat greater than normal in the other three instances   Eppinger, von Papp and Schwarz

(1924) reported five patients with normal values and five with supernormal values for this function Of the nine persons with congestive heart failure studied by Eppinger, Kisch and Schwarz (1927), six had larger and three had smaller cardiac outputs per minute than did their control subjects Kroetz' (1930) patients were studied both when congestive failure was present and absent and in general no significant difference was found Similarly, inconstant results were reported by Kimmonth (1928) and by Bansi and Groscurth (1931)

Aside from the fact that the investigations which have been cited have not yielded uniformly low values for the cardiac output as is demanded by the forward-failure hypothesis, the results need not, in any case, be discussed further for the reason that most of the figures were obtained by methods of doubtful accuracy A systematic discussion of these methods is beyond the scope of the present paper This problem has been studied by Grollman (1932), who has pointed out that most of the methods do not yield accurate results even in normal subjects Measurements made by them in persons with congestive heart failure are therefore open to very serious question In recent years other procedures, which appear to yield dependable results, even in the presence of congestive failure, have been devised These are (1) The direct Fick method, (2) the injection method, (3) the ethyl iodide method, as employed by Starr and Gamble, (4) the venous plateau method, and (5) the acetylene method, when the three-sample technique is used

Data obtained by the direct Fick method This procedure involves the measurement of oxygen consumption and of the oxygen contents of arterial blood and of venous blood obtained by puncture of the right side of the heart Because of the possible dangers involved in puncturing the heart of man, very few observations have been reported by this method Lauter (1930) found subnormal values for the cardiac output per minute in each of three patients with congestive heart failure A similarly low value was found in a patient with complete heart block and with no evidence of congestive heart failure The output per beat was much diminished in the three former subjects, but was not subnormal in the latter subject

Data obtained by the injection method This procedure involves the determination of the concentration curve in arterial blood of vital red

injected intravenously   It was introduced by Hamilton, Moore, Kinsman and Spurling (1932), who checked it against the direct Fick procedure in animals, and against the measured flow through artificial systems and through perfused lungs   Although the values obtained by this method are somewhat higher than those found by other reliable procedures, the difference can probably be ascribed to the conditions under which the method is carried out   Hamilton and his coworkers made observations on a large group of subjects with cardiac disease   In general the output of the heart per minute tended to be low in such patients but no correlation was observed between this function and the clinical state of patients   Some subjects with severe congestive failure had greater cardiac outputs per minute than other persons who were free of congestive phenomena   A more definite correlation existed between the severity of the clinical picture and the degree of diminution in the output per beat, although here again the agreement was not absolute and many exceptions were noted   The most constant abnormality in patients with congestive heart failure was an increase in the intrathoracic blood volume   This function was markedly greater in relation to the output per beat in the persons with congestive heart failure than in subjects who had no congestive phenomena

The findings of Weiss and Robb (1933), who studied patients during attacks of cardiac asthma, were similar   These authors also used the injection method   They were unable to demonstrate any correlation between the cardiac output during the dyspneic seizure and the clinical state   Some of the patients had as great a cardiac output per minute during the severe seizures as during the intervals between attacks   However, the attacks were associated with a sudden increase in the volume of blood in the lungs

Data obtained by the ethyl iodide method   This procedure, as originally introduced, has been shown to be inaccurate   However, when applied according to the technique devised by Starr and Gamble (1927), the results appear to be reliable   Starr and his colleagues (1933) did not study subjects with frank congestive heart failure but made observations on patients who had recently recovered from it   They found that such subjects had on the average lower cardiac outputs than did their control patients, but the differences were not

consistent   Certain patients with advanced myocardial disease had greater cardiac outputs than some normal subjects   In proportion to the oxygen consumption the patients with cardiac disease exhibited lower cardiac outputs than did the control subjects   In a later study Starr and his coworkers (1934) reported a statistical analysis of the results obtained on 204 patients with various disorders and 31 healthy subjects   The lowest values for the cardiac output were obtained in persons with neurocirculatory asthenia and in subjects who had recently recovered from congestive heart failure   Again it was found that many of the cases with advanced cardiac disease had cardiac outputs within the normal range   The authors pointed out that in proportion to their size the hearts of such patients were doing considerably less than the normal amount of work   The importance of this observation will be pointed out in a later section

Data obtained by the venous plateau method   This procedure [Friedman, Clark and Harrison (1934)] involves the determination of the oxygen content of the "mixed" venous blood by drawing successive arterial samples while the patient respires a gas mixture previously brought into equilibrium with the venous blood by repeated rebreathings   The method appears to yield accurate results even in the presence of mild congestive heart failure   However, it is tedious, involves difficult technique and is uncomfortable for the patient   Only a few observations by it have been reported   Grollman, Friedman, Clark and Harrison (1933) reported five patients with mild congestive heart failure who had, by this method, slight to marked diminution in the cardiac output

Data obtained by the acetylene method   This procedure, which was introduced by Grollman (1932) is now being widely used for investigations of the cardiac output in pathological conditions   Its accuracy in persons without circulatory disturbances has been convincingly demonstrated by Grollman   In persons with congestive heart failure, certain additional precautions need to be taken and without them seriously inaccurate results may be obtained   Grollman and his coworkers (1933) demonstrated that twenty seconds or longer may be required in such patients for adequate mixture to take place in the lung-bag system   If the first gas sample is taken earlier than this, erroneous results are likely to be obtained   In certain subjects with

high degrees of pulmonary congestion it is impossible to secure accurate results However, if the three-sample technique [Grollman, Friedman, Clark and Harrison (1933)] is employed, inaccurate results can be detected and discarded, for the procedure of taking three samples and thereby measuring two successive arteriovenous oxygen differences in the same rebreathing, allows one to know whether a homogenous mixture has been obtained in the lung-bag system at the time of the first sample and whether recirculation has occurred at the time of the third sample A more complete discussion of the technique of this procedure is foreign to the purpose of this review, but it should be pointed out that the accuracy of the results obtained by the two-sample acetylene method in patients with congestive failure is open to such grave question that they cannot be accepted On the other hand it has been shown that data obtained by the three-sample acetylene method are not only valid on theoretical grounds, but are in agreement with values arrived at by the venous plateau procedure, which is based on an entirely different principle Cardiac output methods at best are difficult and the neglect of what at first sight may appear to be an unimportant technical detail has led too often in the past to far reaching conclusions based on data of dubious accuracy

A number of studies have been published of the cardiac output in congestive heart failure as measured by the three-sample technique As a rule, to which these are many exceptions, the pulse rate increases and the stroke volume declines during congestive failure Although an occasional patient with congestive phenomena may have a normal value for the cardiac output per minute, this function is usually diminished in such subjects [Harrison, Friedman, Clark and Resnik (1934)] The degree of diminution is ordinarily not very striking, being on the average fifteen to twenty per cent less than the normal value for persons of similar size Since the oxygen consumption is elevated in the majority of persons with congestive heart failure the cardiac output in proportion to the metabolism is considerably diminished The arteriovenous oxygen difference, which is an inverse measure of the cardiac output in proportion to the metabolism, ranges between fifty and seventy cubic centimeters per liter in a normal person (5 to 7 volumes per cent). Considerably higher values are usually found in patients with congestive heart failure, the arteriovenous

oxygen difference varying between sixty and 120 centimeters per liter (6 to 12 volumes per cent) In a given patient recovery from congestive heart failure is frequently associated with a decline in oxygen consumption and in the arteriovenous oxygen difference, the cardiac output per minute remaining unchanged However, in certain individuals the arteriovenous oxygen difference remains constant and the cardiac output declines parallel with the oxygen consumption during improvement In other patients the metabolism undergoes slight or no decrease, the arteriovenous oxygen difference diminishes considerably and a well marked rise in cardiac output occurs as congestive phenomena disappear *No parallelism exists between the severity of the symptoms and the level of the cardiac output, either when considered as such or in proportion to the metabolism*

B *The effect of therapeutic measures on the cardiac output* Of the various methods of treatment which are commonly employed in patients with congestive heart failure, rest is probably the most important When clinical improvement, as shown by loss of edema, diminution in dyspnea, and increase of vital capacity, occurs as the result of rest alone, the cardiac output may or may not change Following rest, with no other therapy except sedatives when necessary for periods of two to six days, slight diminution in the cardiac output occurred in three of four patients studied by Resnik, Friedman and Harrison (1934), the fourth patient exhibiting no change One of these subjects exhibited a considerable decline in the output in proportion to the metabolism The other three patients were inconstant in this regard Three of the four subjects exhibited distinct clinical improvement

The effect of digitalis has been the subject of considerable study In the isolated heart of the frog the output per unit of time may or may not be altered, depending on whether the increased stroke volume does or does not predominate over the diminished rate In the heart-lung preparation no effect of strophanthin on the cardiac output was noticed by Bijlsma and Roessingh (1922) Bodo (1928) likewise found the output unchanged after administering digitalis Plant (1914) found that strophanthin administration was followed by increased amplitude of contraction in hearts previously poisoned by phosphorus These effects were transient, the output returning to the previous

el in a few minutes   Cohn and Steele (1932) gave digitalis to hearts
ich were failing, as shown by a rise in the auricular pressure and a
rease in the output   The drug caused a temporary reversal of
se effects   It should be noted that all of these authors who worked
h the heart-lung preparation found that digitalis diminished the
e of the heart   The importance of this observation will be dis-
sed in a later section

n normal dogs digitalis produces significant decline in the minute
diac output [Harrison and Leonard (1926)] [Cohn and Stewart
28)] [Dock and Tainter (1930)]   Similar results have been found
normal men by Burwell, Neighbors and Regen (1927) and by
wart and Cohn (1932).

n intact animals with various cardiac disorders digitalis may cause
her an increase or a decrease in the output of the heart   Thus,
hn and Stewart observed a marked diminution in dogs with en-
ged hearts due to valvular lesions but without evidence of heart
lure (1928)   Stewart and Gilchrist (1928) produced auricular
rillation in unanesthetized dogs and found that digitalis increased
e cardiac output, which was diminished during the arrhythmia
A number of investigators have studied the effect of digitalis in
tients with congestive heart failure   Using the original ethyl iodide
thod, some authors [Ringer and Altschule (1930)] [Lauter and
umann (1929)] have reported increase in cardiac output, whereas
ders [Kinimmonth (1928)] have observed inconstant effects
pinger, von Papp and Schwarz, employing an indirect Fick oxygen
ocedure, reported diminution in the cardiac output following the
ministration of digitalis, while Ewig and Hinsberg (1931), using the
rbon dioxide procedure, failed to find consistent alterations   Stewart
d Cohn studied seven patients and found in six of these definite
e in the cardiac output when digitalis was given   The latter authors
ed the two-sample acetylene procedure, and stated in the description
their methods that the first gas sample was taken after 15 seconds
rebreathing

It has already been pointed out that these procedures are open to
ious question   Patients with congestive heart failure are usually
able to secure homogeneous mixture in a lung-bag mixture with
s than 20 seconds rebreathing [Grollman, Friedman, Clark and

Harrison (1933)] For this reason the results which have been quoted concerning the effects of digitalis on the cardiac output of patients with congestive heart failure cannot be regarded as convincing Friedman, Clark, Resnik and Harrison (1935) studied 22 patients before and after the administration of digitalis They used the three-sample acetylene procedure which, as has been mentioned, appears to give reliable results when certain rigid criteria are adopted Their patients were divided into three groups according to whether clinical improvement was beyond question, was doubtful, or was absent In each of these groups some individuals had an increase, others a decrease and still others no significant changes in the cardiac output following the administration of digitalis Similarly, inconstant changes were found in the cardiac output in proportion to the metabolism *This study indicated clearly that improvement in the clinical state with disappearance or diminution in the severity of congestive phenomena when brought about by digitalis cannot be ascribed to changes in the blood supply to the body tissues* The mechanism whereby beneficial effects are produced by digitalis will be discussed in Section VIII

Aside from rest and digitalis, sedatives and diuretic drugs are perhaps the most generally useful therapeutic measures in persons with congestive heart failure Relatively little is known concerning the effects of sedatives on the circulation of such patients Slight diminution of the cardiac output following the administration of morphine was observed in each of the two individuals studied by Resnik, Friedman and Harrison (1934) The oxygen consumption likewise decreased, the output of the heart in proportion to the metabolism tending to remain unchanged Further studies along these lines are needed before any general conclusions concerning the action of sedatives can be drawn

Observations following the administration of diuretics were reported by Eppinger and his colleagues (1924), and by Stewart and Cohn (1932), but the results cannot be regarded as convincing because of the methods used The eleven patients studied by my colleagues and myself failed to exhibit constant changes in the cardiac output after they had received diuretics [Friedman, Resnik, Calhoun and Harrison (1935)] Evidently the improvement produced by such drugs is not related to any general change in tissue blood supply

The bleeding of patients with congestive heart failure usually results in distinct although slight and temporary diminution in the cardiac output [Resnik, Friedman and Harrison (1934)]   On two occasions I have observed fainting in patients who were bled while in the sitting posture   Both of them exhibited a well marked decline in the cardiac output and each complained of faintness, dizziness and weakness, but neither became more dyspneic

In patients with auricular fibrillation reversion to regular rhythm as the result of quinidine therapy is usually accompanied by a well marked increase in the output of the heart, as was first demonstrated by Smith, Walker and Alt (1930), and was confirmed by Kerkhof and Baumann (1933), and by Resnik, Friedman and Harrison (1934)

The foregoing discussion concerning the effects of therapeutic measures may be summarized by saying that diverse methods of treatment produce no consistently constant alterations in the amount of blood pumped by the heart and that improvement may occur with changes in either direction, or with no change in the cardiac output

C *Cardiac dyspnea in relation to the forward-failure hypothesis.* Space does not permit a detailed discussion of the mechanism of the several types of cardiac dyspnea   This subject has been reviewed elsewhere [Harrison (1935)]   However, since this symptom is the most important subjective manifestation in the majority of patients suffering from congestive heart failure it is obvious that any satisfactory concept of the pathogenesis of this syndrome necessarily includes an adequate explanation of dyspnea   Traube (1871–8) attributed cardiac dyspnea to congestion of the lungs, which caused the capillaries to encroach upon the air spaces (*Lungenschwellung*), thereby interfering with the ventilation and causing defective aeration of the blood   This theory was modified by von Basch (1891), who thought that the decreased aeration was due to rigidity of the lungs (*Lungenstarre*) as a consequence of congestion   However, Kraus (1897) demonstrated that the alveolar carbon dioxide pressure was subnormal in persons with cardiac failure   This observation, which was confirmed by Porges (1910), indicated that cardiac dyspnea could not be dependent upon an excess of carbon dioxide in the blood as the result of inadequate pulmonary ventilation, and the idea of carbon dioxide acidosis has been further discredited in recent years

by Eppinger, von Papp and Schwarz (1924), Peters and Barr (1921), Fraser, Harris, Hilton and Linder (1928) and Cullen, Harrison, Calhoun, Wilkins and Tims (1931) Their studies are in general agreement in indicating that increased hydrogen ion concentration of the arterial blood as a result of carbon dioxide retention is an exceptional finding in patients with cardiac dyspnea and is encountered only in moribund subjects and in persons with extensive pulmonary disease On the other hand a decrease in the carbon dioxide tension is a fairly frequent finding in severely dyspneic patients

Lack of oxygen in the arterial blood has likewise been indicted as the cause of cardiac dyspnea and this mechanism undoubtedly plays a role in patients suffering from dyspnea associated with pneumonia, pulmonary infarction, and severe edema of the lungs However, since cardiac dyspnea is ordinarily associated with normal or nearly normal values for the arterial saturation, and since it may exist in severe form in patients whose blood is almost 100 per cent saturated [Eppinger, Kisch and Schwarz (1927)] [Calhoun, Cullen, Harrison, Wilkins and Tims (1931)], it is evident that arterial anoxemia is not the fundamental cause Certain patients with congestive heart failure are benefited by being placed in an oxygen chamber, as has recently been shown by Barach (1931) and his coworkers [Barach and Richards (1931)] [Barach and Levy (1934)] The mechanism of this improvement in patients with a severe anoxemia is clear, but the reasons for such a beneficial action in subjects with an arterial oxygen saturation of 90 or more have not yet been demonstrated If the improvement in dyspnea were the direct result of the relief of such a slight degree of anoxemia, one would expect it to come on immediately, whereas, actually it is apparently delayed for 24 hours or more Possibly the beneficial effects in such patients are due to the direct effect on the heart muscle of the increased oxygen tension of the blood Resnik (1925) showed that anoxemia of a degree which had no effect during the normal heart rate produced changes in auriculoventricular conduction during tachycardia It is also possible that increase in tissue oxygen tension may reduce the venous return and thereby diminish the load on the heart In any case, since such a slight degree of arterial anoxemia produces no respiratory discomfort whatever in normal subjects, it can evidently be at most only an added factor and not the fundamental one in the causation of cardiac dyspnea

Mackenzie (1913) (1925), Lewis (1933) and many others have ascribed respiratory distress to a deficiency in cerebral blood flow The data which have already been noted in regard to the cardiac output of patients with congestive heart failure make this highly improbable, for they indicate that disappearance of congestive phenomena, and hence of dyspnea, is not regularly associated with an increase in this function   Still more convincing evidence against this conception of the mechanism of cardiac dyspnea is to be found in the investigations of Cullen (1931), Calhoun (1931), and their coworkers   These investigators studied the effect of exercise and of posture on the gases and the hydrogen ion concentration of arterial and internal jugular venous blood of patients with cardiac dyspnea The values found for the arteriovenous oxygen difference were similar to those reported by Lennox (1930) in normal subjects   Neither the dyspnea of mild muscular effort nor that produced by the assumption of the recumbent posture was accompanied by significant changes in the arteriovenous oxygen difference, carbon dioxide tension or the hydrogen ion concentration   Unless one is willing to make the unlikely assumption that the metabolism of the brain is decreased both by the performance of muscular exercise and by the shift from the sitting to the recumbent posture these observations appear to constitute convincing evidence against the hypothesis which ascribes cardiac dyspnea to an inadequate cerebral blood flow

D *Cardiac edema in relation to the forward-failure hypothesis* Since it has been demonstrated that lack of oxygen causes capillary dilatation [Krogh (1929)] and makes the capillary walls more permeable [Landis (1928)], some authors have assumed that cardiac edema is due to anoxemia as a result of diminished blood flow and increased oxygen utilization   The capillary walls are normally freely permeable to water and to small molecules   Hence, edema as a result of an increase in permeability can only be brought about by a transudation of protein molecules from the capillaries into the tissue spaces with a rise in the colloid osmotic pressure of the extracapillary fluid and a diminution in the counteracting colloid osmotic pressure of the blood That such a mechanism is operative in the edema of inflammation and in certain cases of acute nephritis is shown by the high protein content of the tissue fluid [Schade (1927)]   Occasionally patients with con-

gestive heart failure may have protein rich edema fluid but such is not usually the case   In most of the cases studied by Haas (1921), Youmans (Personal communication), Gilligan, Volk and Blumgart (1934), and by Bramkamp (1935), the tissue fluid protein was 0 3 per cent or less   These observations indicate clearly that increased capillary permeability is not the primary and essential factor in the production of cardiac edema although such a mechanism may play a part in exceptional instances   The forward-failure hypothesis therefore fails to explain edema just as it fails to account for dyspnea

E   *Experimental diminution in the cardiac output* may be brought about by hemorrhage [Harrison and Blalock (1927)] [Blalock (1927)] by trauma to the intestines [Blalock (1931)] or to muscles [Blalock (1930)], by burns [Blalock (1931)], by spinal anesthesia [Burch and Harrison (1930)], and by various other procedures which induce peripheral circulatory failure   Under such conditions the cardiac output may reach very low levels   However, the experimental animals do not exhibit dyspnea except when moribund, and do not present the other important phenomena seen in patients with congestive heart failure

F   *The manifestations produced by a decrease in cardiac output* are those of circulatory collapse or shock   The chief subjective phenomenon is weakness, which may progress to unconsciousness   Objective signs are ashen pallor, cold moist skin, diminished body temperature, rapid feeble pulse, decreased blood pressure and pulse pressure, and heart sounds which resemble each other in quality ("tic-tac sounds")   The circulation in such states has been studied by Blalock and his colleagues [Blalock (1927)] [Blalock and Bradburn (1927)] [Blalock (1930)], and they have been shown to be dependent on a decrease in the cardiac output   This may be brought about either by conditions which decrease the blood pressure (primary or neurogenic shock—such as syncope or spinal anaesthesia) or by agents which diminish the blood volume (secondary or hematogenic shock)   In either case the result is inadequate venous return and consequent decrease in the output of the heart which can expel no more blood than it receives   The clinical picture so produced is dependent on deficiency of the blood supply to the tissues but it is not the clinical picture of congestive heart failure

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... acute myocardial damage
... or diphtheritic myocardi-
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... The evidence which ... clearly that the syndrome of ... is not dependent on a defective blood supply ...

... No reliable data exist to support such an assumption. The ... of cardiac ... on which it has been based have been ... by methods which have been shown by subsequent work to be ... and even by those methods consistent changes in the ... output have not been found.

... Data exist which have been obtained by several reliable methods ... on several entirely different principles. These data are in ... agreement in indicating that although the output per minute ... heart is usually subnormal in persons with congestive heart ... this function may be within normal limits in such cases and ... persons with no congestive phenomena may have equally low ... values for the cardiac output.

(3) No parallelism exists between the severity of the congestive manifestations and the level of the cardiac output

(4) Certain procedures, such as the administration of digitalis, may produce improvement without causing measurable changes in the cardiac output

(5) Some therapeutic measures, such as rest and venesection, may cause clinical improvement and a decrease in the cardiac output

(6) The forward-failure theory fails to explain the mechanisms of dyspnea and of edema, which are, generally speaking, the two most striking clinical manifestations of the syndrome

(7) Experimental diminution in the cardiac output produces a clinical picture resembling that of shock or collapse, but does not produce a syndrome like that of congestive heart failure

V THE BACKWARD-FAILURE HYPOTHESIS

The following paragraphs are quoted from a discussion which has been published elsewhere (Harrison, 1935)

"In its simplest form the 'back-pressure' theory may be summarized as follows Overwork of the heart leads to enlargement, which usually is brought about by both hypertrophy and dilatation of those portions of the heart which are subjected to the increase in work If dilatation of a chamber becomes extreme there results a rise in the pressure in the veins which supply the affected side of the heart The increased venous pressure leads to congestion of the organs drained by these veins Thus, in a patient with mitral stenosis there is hypertrophy and dilatation of the left auricle with an eventual increase in the pressure and congestion of the lungs Because the pulmonary arterioles have little or no 'tone' the pulmonary arterial pressure is also raised The right ventricle now being subjected to overwork undergoes hypertrophy and dilatation After a time the dilatation may become marked Then a relative insufficiency of the tricuspid orifice may develop with a rise in the right auricular pressure Even though the tricuspid valve remains competent the increase in pressure in the right ventricle will tend to offer resistance to the passage of blood from the right auricle Consequently, a rise in pressure in the latter chamber occurs Eventually the systemic venous pressure rises, and as a result the symptoms of 'right-sided' failure develop venous congestion, engorgement of the abdominal viscera, edema and, in some cases, ascites and hydrothorax

"In patients with hypertension the story is essentially the same except

hat pulmonary congestion, instead of occurring almost coincidentally with
he development of the lesion, does not develop until later in the picture,
fter the left ventricle has 'failed' The latter chamber, being the strongest
art of the heart, has great reserve power and therefore a patient may have
or years a lesion imposing a strain on the left ventricle and never exhibit
ny signs of pulmonary congestion Eventually, however, the over-
orked left ventricle dilates sufficiently to cause a rise in the pressure in
he left auricle and from this point onward the sequence of events is rather
milar to that in patients with mitral stenosis 'Rather similar' but not
lentical, because in the one case—mitral stenosis—the rise in pulmonary
ressure and consequent strain on the right ventricle, being due to a slowly
rogressive obstructive lesion of the mitral valve, develop gradually,
hereas, in the other instance—hypertension—congestion of the lungs,
eing due to increase in the degree of dilatation of the left ventricle, may
ome suddenly

"From this line of reasoning one would expect the clinical phenomena
f pulmonary congestion to be present at a relatively early stage of the
nalady in patients with mitral stenosis and at a much later stage in sub-
ects with hypertension or aortic insufficiency That this is actually the
ase is demonstrated by the fact that in the former cases decrease in vital
apacity occurs early, in the latter cases late, in the progress of the disease

"It is evident that the 'back-pressure' theory is fundamentally opposed
o the 'forward-failure' (diminished output) theory The former hypothe-
s states that the symptoms develop in the organs which feed blood toward
he failing chamber of the heart, the latter hypothesis indicates that the
ymptoms develop in the organs which receive blood from the failing
hamber According to the 'back-pressure' idea the essential phenomenon
s an alteration in intracapillary pressure, whereas, the 'forward-failure'
hesis postulates a change in volume-flow as the outstanding feature

"Does the 'back-pressure' theory necessarily imply diminution in cardiac
utput? If by the latter phrase one means that the output of the heart in
roportion to the metabolic needs, is subnormal continuously throughout
he duration of congestive heart failure, the answer is in the negative
Iowever, if by diminished cardiac output one implies reduction in the out-
ut per beat for a few seconds or minutes at a time, the answer is in the
ffirmative

"The last sentence can best be explained by an example Let us take a
ase of hypertension and assume that the left ventricle is hypertrophied
nd dilated but has not yet 'failed,' i e, the pressure in the left auricle
s normal The output of each ventricle is, let us assume, 40 cubic centi-

meters per beat, and the minute volume is 3 2 liters, the pulse rate being 80 Now if the left ventricle becomes a little more fatigued it may expel only 39 cubic centimeters per beat For a short period of time, however, the inflow into the left ventricle will continue to be 40 cubic centimeters per beat and hence after ten beats it contains 10 cubic centimeters more blood at the end of systole than it did heretofore As the left ventricle becomes more dilated the pressure in it rises a little toward the latter end of diastole Hence, the left auricle, which still has an unaltered pressure curve, now expels only 39 cubic centimeters per beat into the left ventricle—the rate of flow being obviously affected by the difference in pressure in the two chambers But the left auricle is still receiving 40 cubic centimeters of blood at each heart beat If it is expelling only 39 cubic centimeters it is retaining one cubic centimeter at each beat Since the left auricle is very distensible it may retain considerable blood without a rise in pressure, but eventually its pressure will rise Let us assume that the time required is that of thirty heart beats The difference in pressure between the two chambers is now the same as it was in the beginning, and hence not 39 but 40 cubic centimeters of blood now pass from the left auricle to the left ventricle during each diastole But the latter chamber is now able to beat a little more powerfully because of its greater diastolic length, i e , dilatation Hence, it again expels 40 cubic centimeters per beat

"The conditions in the pulmonary circuit undergo change, however As soon as the pressure in the left auricle rises less blood enters the left auricle than formerly But since the right ventricle is still expelling 40 cubic centimeters of blood at each heart beat, the pressure in the lesser circuit rises as blood accumulates in the lungs Because of their sponge-like consistency, and also because their capillaries are unique in being surrounded by air, it probably takes a relatively large volume of blood to cause a small rise in the pulmonary vascular pressure Let us assume that 200 cubic centimeters of blood would suffice (This value is purely arbitrary but seems of reasonable magnitude)

"This rise in pressure now corresponds in degree to the increase in the pressure in the left auricle As a result 40 cubic centimeters of blood again enter the left auricle at each beat So far as volume flow is concerned the conditions are now exactly the same as they were in the beginning, each ventricle is now expelling 40 cubic centimeters per beat and, if we assume that the pulse rate has remained constant, the cardiac output per minute is exactly what it was in the beginning In order that this could occur, however, the following changes have taken place

1 A temporary decrease in the output of the left ventricle

2 An increase in the degree of dilatation of the left ventricle

3 An increase in the size of the left auricular cavity and in the left auricular pressure

4 An increase in the pulmonary vascular pressure and in the volume of blood in the lungs

5 A diminution of vital capacity because of (a) the greater content of blood in the lungs and (b) the resulting increase in rigidity (for the lungs can be regarded as erectile tissue)

6 A slowing of the average velocity of blood flow in the lungs—for the size of the stream bed has increased but the volume-flow has not changed

7 An increase in the work of the right ventricle because of the rise in pulmonary pressure The ventricle consequently dilates and, after a time, may become hypertrophied

8 A loss of 240 cubic centimeters of blood from the peripheral circulation (10 cubic centimeters into the left ventricle, 30 cubic centimeters into the left auricle, and 200 cubic centimeters into the lungs) Hence, if the amount of blood in the peripheral circulatory system is to be as great as before, the total blood volume must increase by 240 cubic centimeters

"From such an example it can be seen that even a mild degree of failure of the heart leads to rather complex changes in the various circulatory functions It is also evident that a reduction of the cardiac output, even though temporary and of such small magnitude as to be entirely without significance from the standpoint of tissue blood supply, may have an important and lasting effect on various other circulatory functions

"If the back-pressure theory is correct it would seem that the explanation of the clinical manifestations of congestive heart failure should not be sought in the cardiac output but rather in the other functions, such as the venous pressure, the blood volume, and the velocity, as distinguished from the volume of blood flow It is one thing to assume a set of conditions as I have done, and quite another thing to demonstrate that they exist in the patient If such alterations as the 'back-pressure' hypothesis postulates do not occur, then the theory must be false, if it can be shown that such changes do occur its validity will be supported "

The implications of the back-pressure theory The considerations which have been mentioned allow the formulation of certain propositions which must hold good if the back-pressure hypothesis is correct These propositions are as follows

1 The heart does not necessarily fail as a whole and congestive phenomena may occur either independently or concurrently in the systemic and pulmonary vascular beds

2 Dilatation of the heart should be demonstrable in all cases of congestive heart failure

3 The volume of blood in the lungs must necessarily be increased in patients with failure of the left side of the heart

4 The velocity of blood flow through the lungs must be decreased in such patients

5 In patients with failure of the right side of the heart the venous pressure must be elevated

6 The total volume of circulating blood must be greater than normal in patients with failure of both sides of the heart

7 The cardinal manifestations of congestive heart failure, such as dyspnea and edema, must be explainable on the basis of this hypothesis

We may now consider the evidence bearing on these several propositions

A *Does failure of one side of the heart alone occur?* This question, which was mentioned in the preceding section, now needs to be considered in more detail   The evidence bearing upon it is of two general types—clinical and pathological   Patients with advanced congestive failure due to the common types of cardiac disease, which are usually of such a nature as to place the primary strain on the left side of the heart, almost always state that their first symptom was dyspnea on exertion followed after a varying period of time by dyspnea at rest, and at a later stage by edema   As will be mentioned later, there is convincing evidence which indicates that edema is due to congestion in the systemic vascular bed, and equally convincing evidence exists which demonstrates that the most important factor in the production of cardiac dyspnea is congestion of the lungs   This order of the development of symptoms is therefore exactly what would be expected to occur—as the result of a lesion which imposes an initial strain on the left side of the heart and only secondarily causes right-sided failure consequent to the increased pressure in the pulmonary circuit

Further clinical evidence along the same line is afforded by the investigations of Weiss and Robb (1933), who demonstrated by the

injection method that paroxysms of cardiac asthma are associated with a sudden increase in the volume of blood in the lungs   It has also been shown both by Blumgart and Weiss (1928–29) and by Hitzig, King and Fishberg (1935), that pulmonary congestion, as indicated by a diminution in the velocity of the flow of blood through the lungs, may occur in the absence of systemic congestion, as tested by measurement of venous pressure

Observations such as those which have been cited appear to constitute conclusive evidence that unilateral heart failure may occur If further evidence is needed it can be readily found at the autopsy table   Although in subjects dying of the ordinary types of cardiac disease enlargement of both sides of the heart and passive congestion in both the systemic and pulmonary vascular beds are found, there are certain exceptional instances which throw light on the question at issue   Thus, in a patient recently observed with malignant hypertension and uremia, cardiac enlargement had been noted for several months but no signs of congestive failure had appeared   She had never complained of dyspnea and was able to lie flat in bed without discomfort until within a few hours of death, which occurred as the immediate result of an attack of acute edema of the lungs which was accompanied by severe respiratory distress   At autopsy the left ventricle was much enlarged, the lungs revealed acute passive congestion and edema, the right ventricle was neither hypertrophied nor dilated, and none of the organs except the lungs showed congestion Such cases, which are not rare, indicate clearly that left-sided heart failure, which was frequently discussed in medical literature fifty years ago but has fallen into disrepute in recent years in the English-speaking countries, is an important clinical syndrome   Similar conclusions have been arrived at in recent publications by White (1933), as well as by the authors mentioned in the preceding paragraph

Subjects exhibiting pure right-sided heart failure are perhaps less common, but the condition is nevertheless well known   I have observed three patients with the syndrome known as *cor pulmonale*, who were studied during life and later subjected to post-mortem examination   These individuals had extensive chronic pulmonary fibrosis of many years duration   They exhibited rather intractable edema, marked cardiac enlargement, severe cyanosis, clubbing of the

fingers, striking venous distention, and enlargement of the liver In spite of the marked arterial anoxemia, dyspnea at rest was not a prominent symptom   Orthopnea was practically absent, the subjects complaining of a sense of fullness in the head rather than dyspnea when they were recumbent   Two of the patients had typical spasmodic bronchial asthma, but none of them had cardiac asthma   The electrocardiograms revealed in each case preponderance of the right ventricle over the left   At autopsy these subjects had marked hypertrophy and dilatation of the right ventricle without enlargement of the left ventricle, which was atrophic   The lungs were not congested but the abdominal viscera revealed typical chronic passive congestion of high degree

A somewhat similar clinical picture was noted in a patient reported by Robinson and Burwell (1928), in a patient with arteriosclerosis involving the coronary branches to the right ventricle only   Both clinically and at post-mortem examination the congestive phenomena were limited to the systemic vascular bed   The right ventricle revealed dilatation of extreme degree, while the left ventricle was normal

Patients with congenital heart lesions, which are usually of such a nature as to involve the right side of the heart primarily, likewise frequently show a striking preponderance of systemic over pulmonary congestion, and at autopsy enlargement may be found to be limited to the right ventricle   Such facts can only be interpreted on the assumption that heart failure may at times involve the right side alone   The differences between the clinical picture in such cases and in patients with cardiac asthma can readily be accounted for by the back-pressure hypothesis but remain totally inexplicable on the basis of the forward-failure theory, which ascribes the symptoms of congestive heart failure to a single fundamental cause—diminution in tissue blood supply

B   *The relation of dilatation of the heart to congestive heart failure* The backward-failure theory involves the assumption that congestive phenomena, when not directly dependent on a valvular lesion, as for instance in the case of pulmonary engorgement associated with mitral stenosis, are brought about by dilatation of one of the ventricles   If this interpretation is correct one should find dilatation of the left

ventricle regularly in association with pulmonary congestion and dilatation of the right ventricle in all subjects with systemic engorgement

The evidence on this point is again of two types—clinical and pathological Since enlargement of the heart to the right is a sign of dilatation of the right auricle, and since this is a constant finding in patients with systemic engorgement, and further, since such subjects at autopsy practically always exhibit a right ventricle with an abnormally large cavity, it may be stated that as regards the right side of the heart, this implication of the back-pressure hypothesis is fulfilled However, as regards the left side of the heart the pathological findings are less convincing Although patients with aortic insufficiency and pulmonary congestion regularly show dilatation of the left ventricle at autopsy, this is not the case in all subjects with pulmonary engorgement secondary to hypertension At post-mortem examination such individuals exhibit left ventricular hypertrophy but the cavity of the left ventricle is sometimes small even though pulmonary congestion has been present During life the physical signs as well as the shape of the roentgenographic cardiac shadow point toward dilatation of the left ventricle and it is conceivable that this cavity may become smaller during the last moments of life, or even after death, but until such changes are demonstrated, the existence of such instances constitutes an objection to the acceptance of the back-pressure hypothesis

The importance of cardiac dilatation in relation to congestive heart failure has been doubted [Christian (1928)] because of the fact that changes in the clinical state are not regularly accompanied by outspoken alterations in the size of the heart However, it must be remembered that clinical methods for the detection of heart size are crude and that studies made by careful roentgenographic methods will usually reveal a measurable shrinkage of the cardiac shadow with clinical improvement Thus, Cohn and his co-workers (1924) (1928) (1932) demonstrated that digitalis decreases the size of the heart both in patients with auricular fibrillation and in those with regular rhythm Unless especially careful technique is used one may fail to demonstrate alterations in the heart size as congestive failure disappears, but this is not surprising in view of the variations in the heart

shadow which occur during respiration and with the heart beat Even when the time of the cardiac cycle at which the film is exposed is controlled, confusing results are introduced by the fact that the auricle is filling most rapidly during systole [Hamilton (1930)] Furthermore, a difference of only a few millimeters in the diameter of a ventricular cavity may indicate a marked difference in contents, for the cavity, being roughly spherical, tends to vary as the cube of its radius

These considerations explain why cardiac dilatation may be difficult to demonstrate in all patients with congestive failure Objections to the back-pressure idea based on this ground seem untenable when it is recalled that in the heart-lung preparation, where the size of the ventricular cavities can be measured directly, the development of heart failure is invariably associated with progressive dilatation [Markwalder and Starling (1913)] [Patterson, Piper and Starling (1914)] [Starling (1918)]

Enlargement of the ventricular cavities may produce congestive phenomena by two possible means In certain instances regurgitation through the auriculoventricular orifices apparently occurs However, since murmurs which appear during congestive failure and disappear with improvement are not usually observed, and since, as regards the tricuspid valve, the veins usually reveal no striking systolic pulsation, it seems probable that regurgitation is not ordinarily of much importance This conclusion is in keeping with the opinions of Mackenzie (1921) and Lewis (1933), whose views on the subject have already been quoted (page 260)

It is unjustifiable however to conclude, as many British and American clinicians have done, that the back-pressure hypothesis is invalid, because regurgitation through the auriculoventricular valves does not occur regularly in patients with congestive heart failure Even though the valves are functioning normally, ventricular dilatation may offer an impediment to the inflow of auricular blood The ventricular musculature is somewhat similar to a rubber band which may be stretched with ease to a certain point but which, once the limits of elasticity are approached, offers increasing resistance to further distention Hence, as residual blood accumulates in the ventricle a point will be reached beyond which further dilatation will progres-

sively tend to interfere with the inflow of blood from the auricle
This fact—that back-pressure may occur in diastole as the result of
resistance to filling, as well as in systole, if the auriculoventricular ring
is stretched—is of fundamental importance in the mechanism of con-
gestive heart failure

C *The volume of blood in the lungs in relation to left-sided heart
failure*   The studies of Peabody and his associates (1915 to 1922)
established clearly the relationship between congestive failure and
diminution in the vital capacity   That this functional change is
dependent on engorgement of the lungs was indicated by the observa-
tions of Drinker, Peabody and Blumgart (1922), who showed that
compression of the pulmonary veins of cats caused diminished dis-
tensibility of the lungs   More direct evidence has been obtained
by the observations of Hamilton, Moore, Kinsman and Spurling
(1932), and of Weiss and Robb (1933), with the injection method.
These authors found a mark increase in the intrathoracic blood volume
in patients with cardiac dyspnea

D *The velocity of the pulmonary blood flow in relation to left-sided
heart failure*   The time required for a complete circuit of the blood
to occur was measured by Koch (1922), who injected fluorescin into
a vein of one arm and collected repeated samples of venous blood from
the opposite arm   His patients with severe congestive heart failure
had circulation times of 30 to 63 seconds, as compared with an average
normal value of 21 seconds

The most extensive studies of velocity of blood flow have been
made by Blumgart and Weiss and their collaborators, and have
recently been summarized by Blumgart (1931)   Their method, which
consists in injecting radium emanations into a vein and in recording
with a suitable detecting device its arrival at some other point in the
vascular bed, appears to be the most objective and accurate procedure
yet employed for the purpose   These authors showed that patients
with well tolerated cardiac lesions had normal or only slightly in-
creased circulation times   Persons who had symptoms on exertion
only displayed prolongation of the circulation time and a diminution
of the vital capacity, but a normal venous pressure   With the
development of systemic congestion the vital capacity and the velocity
of blood flow through the lungs were still further reduced and a rise

in venous pressure occurred   Such a series of events is in accord with
the back-pressure theory in that it indicates the development of pul-
monary congestion prior to systemic congestion   Furthermore, the
observation of Blumgart and Weiss that decrease in vital capacity
and diminution in velocity of blood flow occurred at a relatively later
stage of the disease in persons with syphilitic heart disease than in
individuals with rheumatic lesions is additional evidence in favor of
the back-pressure idea   In the former case, the initial strain being
on the left ventricle, congestion of the lungs cannot occur until there
is failure, i e , marked dilatation of the left ventricle, while in rheu-
matic heart disease the lesion, being usually situated at the mitral
orifice, causes a rise in the left auricular pressure and consequent
congestion of the lungs at a relatively earlier stage of the malady
These observations of Blumgart and Weiss, which have been con-
firmed by Hitzig, King and Fishberg (1935), indicate that the veloc-
ity of blood flow through the lungs is diminished in patients with
failure of the left side of the heart and that it increases with
clinical improvement   This conclusion has sometimes been inter-
preted as indicating that the volume flow, i e , the cardiac output,
undergoes similar changes   However, the velocity of flow is related
not only to the volume-flow but also to the size of the vascular bed
A decrease in velocity may occur in the presence of a constant vol-
ume flow, provided there is at the same time an increase in the size of
the pulmonary vessels

E   *The blood volume in relation to congestive heart failure*   The dem-
onstration that the velocity of the blood flow is diminished in persons
with cardiac failure can be interpreted as indicating a decrease in
the volume-flow, i e in the cardiac output, only if it can be shown that
the size of the stream bed does not change   The best measure we
have of the latter function is the blood volume   Keith, Rowntree
and Geraghty, using their dye method, found a slight increase in blood
volume of persons with cardiac failure (1915)   Brown and Rowntree
(1925) found blood volumes ranging from 104 to 119 cubic centimeters
per kilogram in patients with cardiac failure as compared to values of
72 to 100 cubic centimeters per kilogram in normal persons   Plesch
(1929) reported increase in the blood volume and fall in the hemo-
globin, which he attributed to dilution, as congestion developed

Hitzenberger and Tuchfeld (1929) found that the blood volume was usually greater in decompensated patients, although exceptions were encountered in persons with emphysema

The most extensive studies on the blood volume in cardiac disease have been made by Wollheim (1929)   His normal persons had 75 to 85 cubic centimeters of blood per kilogram of body weight, whereas, persons with well compensated cardiac disease had somewhat lower values—60 to 75 cubic centimeters per kilogram   Patients with congestive heart failure were found to fall into two groups as regards the blood volume, the majority of them having blood volumes of 80 to 120 cubic centimeters per kilogram   A smaller group of patients, especially those with cardiac failure secondary to chronic disease of the lungs, exhibited diminished blood volume, the values being 40 to 60 cubic centimeters per kilogram   Wollheim pointed out that the latter patients could be distinguished clearly from the former group by the absence of orthopnea and the fact that they are not helped by digitalis, which was found to diminish the blood volume The latter observation was in agreement with the previous findings of Schurmeyer (1928), and with the later studies of Mies (1931), who found that strophanthin diminished the blood volume of rabbits, of normal men, and of decompensated patients

The studies of these various authors are in agreement in indicating that patients with congestive heart failure usually have an increase in the blood volume   Further evidence was offered by Bolton and Starling (1910), who found that they were able to obtain, by bleeding, 500 cubic centimeters of blood from a dog with spontaneous chronic cardiac failure as compared to 300 cubic centimeters in a normal dog of the same size

At the autopsy table one observes that patients dying of cardiac failure have an increased amount of blood in the heart, the lungs, the veins, the liver and other organs   By an indirect method, Hamilton, Moore, Kinsman and Spurling (1932) have been able to measure the volume of blood in the heart and lungs of man and these measurements indicate that the intrathoracic blood volume is usually markedly increased and is sometimes more than double the normal amount in persons with congestive heart failure, whereas, patients with compensated cardiac lesions showed a less marked increase, or no increase, in the intrathoracic blood volume

The failure of patients with cardiac disease to exhibit marked weakness and other manifestations of shock is probably related to their compensatory increase in blood volume   Persons with shock not only have subnormal cardiac outputs, but they usually have relatively empty capillaries, whereas, individuals with cardiac failure may occasionally have equally low cardiac outputs, but they have a greater number of open capillaries because of the larger blood volume   The exchange of substances between the tissues and the blood is obviously dependent on the number of open capillaries as well as on the rate of blood flow

F *The venous pressure* Concerning the venous pressure in the lesser circulation no direct data are available   As regards the systemic venous pressure it has been adequately demonstrated by the studies of Eyster and his coworkers (1929), Blumgart and Weiss (1928–29), Schott (1912), and others, that outspoken systemic congestive phenomena are practically invariably associated with a rise in this function

G *Edema in relation to back pressure* Of the several factors which influence the exchange of water between the blood and the body tissues the most important are the colloid osmotic pressure of the blood (tending to retain fluid in the capillaries) and the capillary blood pressure (tending to force fluid through the capillary walls)   The development of edema is favored by a decrease in the colloid osmotic pressure or by an increase in the capillary blood pressure   The former function, while often normal; is sometimes slightly reduced in patients with congestive heart failure [Eppinger, Kisch and Schwarz (1927)] [Bramkamp (1935)], and this reduction may play a role in the causation of edema in certain cases   But the observations which have been cited [Eyster (1929)] [Blumgart and Weiss (1928–29)] [Schott (1912)] indicate clearly that in persons with cardiac edema elevation of venous pressure is a constant finding and that this functional change is the chief cause of the accumulation of water in the tissues   The increase in venous pressure will necessarily impede the circulation through the tissues until such a time as the oncoming arterial blood raises the blood pressure in the capillaries above that in the veins   That this increase in capillary blood pressure directly dependent on an increase in the venous pressure is the essential factor in the production of cardiac

edema is indicated by the observations of Landis and his coworkers (1932)   Other subsidiary factors which may play a rôle in certain cases are decrease in plasma protein as a result of albuminuria or of deficient protein intake, interference with drainage of the thoracic duct when the jugular venous pressure is excessively high, increased capillary permeability consequent to diminished blood flow, diminished mechanical tissue pressure because of previous stretching from massive edema, and excessive intake of water and sodium chloride   However, since all of the latter functional changes are inconstant, it is evident that the increase in venous pressure, which occurs regularly in patients with cardiac edema, is the essential factor   This is in accord with the backward-failure hypothesis

H *Dyspnea in relation to back-pressure*   A detailed discussion of the mechanism of the several types of cardiac dyspnea would lead us beyond the limited field of this review   The following paragraphs are therefore concerned only with certain general principles and the reader is referred elsewhere [Harrison (1935)] for a more complete consideration of the subject

The idea that cardiac dyspnea is primarily of chemical origin (i e , that it is due to changes in blood flow or blood gases) has been disproved (page 272)   It was shown by Harrison, Turley and Calhoun (1931) that in patients with congestive heart failure the degree of dyspnea was proportional to the expression $\dfrac{\text{Ventilation}}{\text{Vital capacity}}$.[1]   Any

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[1] In order to avoid misunderstanding this statement should be explained   Dyspnea, a subjective phenomenon, is not *caused* by a change in these respiratory functions but is the cortical reflection of the same mechanism, which when acting on the lower nervous centers, produces labored breathing, an objective phenomenon   If one excludes from consideration neurotic subjects, in whom subjective manifestations are exaggerated out of proportion to objective responses, then the degree of dyspnea may be determined by measuring the extent to which the breathing is labored   So long as there is no hindrance to the passage of air in and out of the lungs, the respiratory effort is increased in proportion to the closeness with which the actual ventilation approaches the maximum possible ventilation   The former can be determined directly and the latter indirectly (by measuring the vital capacity)   From such observations a rough quantitative estimate of the degree of dyspnea can be obtained from the ratio $\dfrac{\text{Ventilation}}{\text{Vital capacity}}$ However, in persons with respiratory obstruction and in those who are psychoneurotic, the ratio is not a reliable guide to the degree of dyspnea

condition which increases the numerator or diminishes the denominator of this ratio will tend to produce dyspnea

As regards the vital capacity, it has been fully demonstrated by the work of Peabody and his associates (1915 to 1922) that this function declines and rises with the development and disappearance of congestive heart failure   The mechanism of this effect was demonstrated by Drinker, Peabody and Blumgart (1922), who showed in cats that congestion of the lungs produced by compression of the pulmonary veins, caused decreased expansibility   This observation, when taken in conjunction with the fact that decrease in vital capacity is observed only in patients with lesions which impose a strain on the left side of the heart, seems to indicate clearly that congestion of the lungs is the result of back-pressure brought about either by dilatation of the left ventricle or by obstruction at the mitral orifice

It is of interest to note that Corvisart, more than 100 years ago, stressed the importance of congestion of the lungs as the chief cause of cardiac dyspnea   "It is possible that, in the diseases of the heart, the difficulty of breathing proceeds entirely from the mechanical compression of the lungs, by enlargement of the heart, or the evolution of an aneurismal tumor, this is true in some cases, but in a greater number, the difficulty of respiration appears to belong solely to the accumulation of the blood in the vascular system of the lungs, from the embarrassment which it suffers on returning into the cavities of the heart, deranged wholly or partly in their natural organization " [Corvisart (1812)]

Pulmonary congestion may produce either swelling [Traube's *Lungenschwellung* (1871-8)], or rigidity of the lungs [von Basch's *Lungenstarre* (1891)] and either of these effects diminishes the vital capacity and hence tends to increase the respiratory effort involved in maintaining any given level of ventilation   However, if the decline in vital capacity is not extreme, dyspnea may be absent so long as the volume of air breathed is not too great   For this reason many patients with congestive heart failure are free of dyspnea until some functional change occurs which stimulates the breathing and increases the numerator in the ratio $\dfrac{\text{Ventilation}}{\text{Vital capacity}}$ The underlying cause of all of the several types of cardiac dyspnea is congestion of the lungs with

its consequent decline in vital capacity; the immediate causes are to be sought in agents which increase the ventilation

Recent studies have demonstrated clearly that reflex rather than chemical factors are chiefly responsible for the stimulation of breathing in patients with congestive heart failure Of the several reflexes concerned the most important arise in the lungs and reach the central nervous system through the vagus nerves It has been shown [Harrison, Calhoun, Cullen, Wilkins and Pilcher (1932)] [Harrison, Calhoun, Marsh and Harrison (1934)] that congestion of the lungs causes a marked increase in the rate of breathing of dogs, this effect being absent after bilateral vagotomy This reflex is chiefly responsible for orthopnea [Calhoun, Cullen, Harrison, Wilkins and Tims (1931)] because the recumbent posture causes a shift of blood from the abdomen to the thorax The degree of preexisting pulmonary congestion is thereby increased The subsequent decline in vital capacity plus the reflex stimulation of breathing results in a rise in the quotient $\dfrac{\text{Ventilation}}{\text{Vital capacity}}$ and this is accompanied by labored breathing and subjective respiratory distress The same reflex is operative in the paroxysms of cardiac asthma [Harrison, Calhoun and Harrison (1934)], a condition which Weiss and Robb (1933) have shown to be associated with a sudden increase in the amount of blood in the lungs as the result of left ventricular failure The latter authors produced relief of dyspnea by blocking the vagus nerves with procaine hydrochloride.

Patients with congestive heart failure are usually more dyspneic in the late afternoon and evening than in the morning Their vital capacities tend to decline in the evening and at the same time the ventilation usually increases [Harrison, Calhoun, Marsh and Harrison (1934)] Both of these changes are apparently the result of an accentuation of the degree of pulmonary congestion as a result of the greater bodily activity and consequent increased venous return during the day as compared to the night If, as in such patients, the heart failure is predominantly of the left side, the left ventricle is already more dilated than the right and even a slight increase in output of the latter may result in accumulation of blood in the lungs

The mechanism of that type of cardiac dyspnea which occurs in

association with the hyperpneic phase of Cheyne-Stokes respiration is not yet completely understood   Among the factors which play a rôle [Harrison, King, Calhoun and Harrison (1934)] here are (1) the decline in vital capacity, which predisposes the subject to dyspnea, (2) reflex stimulation of respiration as the result of pulmonary congestion, (3) sudden decrease and increase in the irritability of the respiratory center with alterations between the waking and sleeping states, (4) loss of carbon dioxide from the blood as the result of overventilation, (5) arterial anoxemia, (6) changes in the acidity of the blood, occurring as the result of oxygenation and reduction of hemoglobin, and leading to "overshooting" of apnea and of hyperpnea, (9) increase in intracranial pressure as the result of heart failure [Harrison, W G Jr (1933) (1934)]

It seems likely that other functional alterations are also concerned in the production of periodic breathing

When we turn from dyspnea occurring at rest to that produced by exertion, additional mechanisms need to be considered   Under the condition of severe exercise increased acidity of the blood probably plays the dominant rôle in stimulating the breathing   However the increase in ventilation which occurs during and after mild exertion is not accompanied by significant alterations in the gases or acidity of the blood [Cullen, Harrison, Calhoun, Wilkins and Tims (1931)], but has been shown to be of reflex origin   Observations on both man and dogs have shown that respiratory reflexes arise in moving tissues [Harrison, Harrison, Calhoun and Marsh (1932)]   The most convincing of several different types of experiments is the following If the hind leg of an anesthetized dog is completely amputated at the hip joint except for the femoral vessels and the sciatic nerve, rapid passive movements of the extremity will cause an increase in the ventilation   The effect is not altered by clamping the femoral vessels but is abolished by cutting the sciatic nerve or by section of the spinal cord   The increase in breathing produced by muscular effort therefore appears to be partly dependent on reflexes arising in the moving parts

A second mechanism which is concerned in the respiratory response to exertion is increase in venous pressure [Harrison, Harrison, Calhoun and Marsh (1932)] [Harrison, Harrison and Marsh (1932)]   Bain-

bridge (1915) showed that a rise in this function caused a reflex increase in the pulse rate, the afferent pathway being through the vagus nerves   Recent observations have demonstrated a similar reflex effect on respiration as the result of an increase in pressure in the great veins and the right auricle   This observation probably explains the fact that during mild exertion the increase in ventilation in persons with congestive heart failure is greater than in normal persons, for Schott (1912) has shown that the rise in venous pressure produced by effort is much greater in the former than in the latter subjects

The mechanism of dyspnea produced by mild exercise may be summarized as follows   Even at rest the patient with congestive heart failure has pulmonary engorgement with its two-fold effects—decrease in vital capacity and reflex respiratory stimulation   His respiratory reserve is thereby encroached upon   When he performs work he has further respiratory stimulation—just as a normal person has—from the moving parts, and the ventilation increases   However, because his heart is less able to take care of the oncoming blood, his venous pressure rises more than that of a normal subject and an additional reflex stimulation of breathing occurs   The increase in ventilation is therefore disproportionately great and the ratio $\dfrac{\text{Ventilation}}{\text{Vital capacity}}$ reaches a high level   In this situation the stimulation of the lower nervous centers is responsible for the labored breathing and that of the cortical centers causes dyspnea

Such are the chief mechanisms responsible for the several types of dyspnea occurring in patients with cardiac disease   Obviously, these are not the only factors concerned   Increase in cerebrospinal fluid pressure plays a rôle in certain patients, as does arterial anoxemia   But the mechanisms discussed are the chief ones and of them the most constant are the decrease in vital capacity and the reflex increase in breathing as the result of engorgement of the lungs

Dyspnea is then, in the main, to be ascribed to pulmonary congestion as a result of "back pressure" from the left side of the heart   The increase in pulmonary pressure eventually leads to failure of the right ventricle and edema, but dyspnea may occur without failure of the right ventricle   Dyspnea usually precedes edema because the underlying disease process ordinarily imposes the initial strain on the left side of the heart

I *The mechanism of cyanosis*   As Lundsgaard and Van Slyke (1923) pointed out, cyanosis may be produced by any condition which increases sufficiently the amount of reduced hemoglobin in the minute vessels of the skin   Such conditions are (a) arterial anoxemia, (b) decrease in the amount of blood passing through the capillary per unit of time, with consequent increased utilization of oxygen from the blood, and (c) dilatation of the capillaries (when not accompanied by an increase in blood flow)   Each of these different mechanisms may be active in the production of cyanosis in patients with heart failure

Diminished oxygen content of the arterial blood occurs in patients who have pneumonia, pulmonary edema, infarctions of the lungs, bronchiectasis, or severe emphysema, and also in subjects with those types of congenital heart disease which produce a right to left shunt In these conditions the cyanosis is likely to be marked and the color is a deep purple   Marked diminution in the output of the heart with a decrease in the oxygen content of the venous blood and an increase in the mean oxygen unsaturation of the capillary blood may also produce cyanosis [Lundsgaard and Van Slyke (1923)]   Cyanosis due to this mechanism is likely to be associated with an ashen tint of the skin such as occurs in patients with coronary thrombosis and other types of acute cardiac collapse, as well as in states of peripheral circulatory failure   Lundsgaard and Van Slyke emphasized the fact that at any given level of capillary oxygen unsaturation the presence or absence of cyanosis will depend on the volume of the capillary bed Goldschmidt and Light (1925) have shown that the cyanosis which occurs in dependent extremities is not associated with alterations in the oxygen content of the blood, but is due to stasis because of the local increase in venous pressure and consequent relative increase in the size of the venules (which contain bluer blood) as compared with the size of the capillaries   Of these several factors which may produce cyanosis in patients with congestive heart failure, the latter, which is dependent on back pressure, is perhaps the most common and probably accounts for the cyanosis in those patients who exhibit neither the intense purplish color of arterial anoxemia nor the ashen bluish pallor of circulatory collapse   Frequently, cyanosis may be due to a combination of the three mechanisms which have been mentioned

J *Tachycardia* occurs in the majority of patients with congestive heart failure in whom the heart is not under the influence of drugs The observations of Bainbridge (1915), which demonstrated that a rise in venous pressure caused reflex increase in the rate of the heart, the effect being abolished by bilateral vagotomy, offer a satisfactory explanation of this phenomenon Tachycardia in patients with congestive heart failure therefore appears to be dependent on back pressure

The relationship of backward failure and subsequent engorgement to such clinical manifestations as *venous distention* and *enlargement of the liver* is too obvious to require comment

K *Objections to the backward-failure theory* From time to time various investigators have interpreted certain observations as casting doubt on the validity of the backward-failure theory Although Corvisart's idea that cardiac dyspnea was dependent on congestion of the lungs seems to have been generally accepted, it was assumed [Traube (1871-8)] [von Basch (1891)] that this interfered with the ventilation of the blood The demonstration that many dyspneic patients with congestive heart failure had no significant excess of carbon dioxide or marked lack of oxygen in the arterial blood [Fraser, Harris, Hilton and Linder (1928)] [Cullen, Harrison, Calhoun, Wilkins and Tims (1931)] [Calhoun, Cullen, Harrison, Wilkins and Tims (1931)] seemed to be important evidence against pulmonary congestion as the cause of dyspnea, and hence against the whole back-pressure idea However, this objection is no longer valid, in view of the demonstration that the most important factor in the production of cardiac dyspnea is reflex stimulation of breathing as a result of congestion of the lungs

A second obstacle to the acceptance of the back-pressure theory, namely, the absence of evidence of regurgitation through the auriculo-ventricular valves in the majority of patients with congestive failure has already been discussed (page 283), and it was pointed out that this objection is based on an inadequate conception of the back-pressure mechanism, which may operate by resistance to the diastolic filling of the ventricle and a rise in auricular pressure, even though the valves continue to function normally The most serious objection to the backward-failure conception is the fact, already mentioned, that

certain patients who present pulmonary edema during life, and who have at autopsy congestion and edema of the lungs, may fail to show dilatation of the left ventricle at post-mortem examination   Since the validity of the whole idea depends on ventricular dilatation this point is an important one   However, in view of the almost overwhelming strength of all the evidence in favor of the back-pressure idea, it is probably justifiable to assume that future work will furnish an adequate explanation for the absence of left ventricular dilatation after death in cases of the type under discussion

L   *Summary of the back-pressure hypothesis*   The evidence which has been discussed leads to the following conclusions   Left-sided failure with pulmonary congestion and right-sided failure with systemic congestion may occur independently of each other (although they often coexist)   Dilatation of one or more chambers of the heart appears, in so far as can be judged by clinical and roentgenographic methods, to be present during life in all cases, and is found at post-mortem examination in the great majority of instances   In patients with left-sided failure there is an increase in the volume of blood in the lungs and a diminution in the velocity of the pulmonary blood flow Persons with right-sided failure exhibit distention of the veins with an increase of venous pressure   The circulating blood volume is increase in subjects with advanced cardiac disease and failure of both sides of the heart   Dyspnea and edema, the two most obvious and striking clinical manifestations of the congestive failure syndrome, can both be accounted for by the back-pressure theory and are not explicable on any other basis   We find then that the implications that are inherent in the back-pressure theory are fulfilled

Two different clinical pictures may result from back pressure Failure of the left side of the heart when it produces only *congestion* of the lungs causes diminution in vital capacity, dyspnea, and in many patients, cough   When the congestion becomes so marked that fluid begins to pass from the capillaries into the alveoli, *edema* of the lungs, as revealed by moist râles, occurs, and if this is of sufficient severity the subject has profuse, frothy expectoration   Hence, it is a fallacy to assume that the lungs are not congested because no râles are heard   The early objective sign of pulmonary congestion is the diminution in the vital capacity and the occurrence of râles indicates

that the congestion is of severe degree   The clinical picture of right-sided heart failure is quite a different one   Here the important manifestations are venous distention, enlargement of the liver, cyanosis, edema and the accumulation of fluid in the body cavities

VI EXPERIMENTAL HEART FAILURE

Thus far the discussion has been centered on heart failure as observed in man   Before accepting the conclusions which have been tentatively arrived at it is important that they be tested in the light of what is known about heart failure produced under controlled experimental conditions   Although no one has yet succeeded in producing chronic congestive heart failure in animals, the observations on the mechanism of acute heart failure throw light on the nature of the more chronic process in man

A *Heart failure as observed in the heart-lung preparation*   Twenty years have passed since the fundamental studies of Starling and his coworkers began to be published, but it is only very recently that clinicians have begun to appreciate their significance   With the heart-lung preparation the rate of the heart, the peripheral resistance, and the venous inflow can be varied at will, while the volume and the output of the heart are measured   Such a procedure is not possible in the intact animal because of the various compensatory mechanisms which are set up when one factor of the circulation is altered   Patterson, Piper and Starling (1914) showed that a sudden increase in the arterial resistance did not change the minute volume or stroke volume except for the first few beats, during which the output was diminished and the heart gradually became dilated because of the residual blood left in it   After a few cardiac cycles the effect of the greater diastolic volume was sufficient to counteract the arterial resistance and the stroke volume returned to the previous normal level   This observation was interpreted as indicating that dilatation enabled the heart to set free more energy because of the increase in surface of the fibers brought about by their increased length   Markwalder and Starling (1913–14) noted that with a constant venous pressure changing the arterial pressure from 50 to 200 millimeters was without effect on the total cardiac output, although the distribution of the blood was altered, the coronary flow being greater and the systemic correspondingly less at the higher pressures.

When the arterial resistance was kept constant and the venous inflow was varied different results were obtained. A rise in venous pressure under these conditions led to a greater filling with increased diastolic fiber length and consequent increase in the systolic discharge. At low levels of venous pressure a relatively slight increase in this function is accompanied by a relatively great rise in the output, but at higher initial venous pressures a greater increase in this function is necessary in order to cause a corresponding rise in the minute volume. According to Henderson and Barringer (1913), the cardiac output and venous pressure remain parallel up to a venous pressure of about 50 millimeters of water, but above this level each further rise in venous pressure is attended by an increasingly smaller rise in the cardiac output.

From experiments such as these the "law of the heart" was formulated by Patterson, Piper and Starling (1914). These authors stated "The law of the heart is therefore the same as that of skeletal muscle, namely, that the mechanical energy set free in passing from the resting to the contracted state depends on the area of chemically active surfaces, i e, on the length of the muscle fibers." This law is of fundamental importance in the proper understanding of the response of the heart to physiological and pathological conditions.

Changes in the cardiac volume are related not only to the heart's mechanical activity but also to its metabolism. Starling and Visscher (1922) studied the oxygen consumption of the cardiac ventricles under various conditions and found it to be determined by the diastolic volume. Hemmingway and Fee (1927) reported similar results for the oxygen consumption of the heart as a whole. These results are of great importance because they indicate that the amount of oxygen used by the heart is dependent not so much on the actual work performed as on the degree of dilatation. Thus a "strong" heart performing a given amount of work with a small diastolic volume will require less oxygen per minute than a "weak" heart which has to dilate in order to do the same work. The dilated heart is therefore an inefficient pump because it can convert relatively less of the energy expended into mechanical work. Similarly, any measure which enables the heart to accomplish its work with a smaller diastolic volume, i e, in a less dilated state, makes the heart more efficient.

This principle is of importance in a proper understanding of the mechanisms whereby digitalis and other therapeutic measures produce benefit

The relation between the pulse rate and the oxygen consumption of the heart was studied by Evans and Matsuoka (1915), who found that for a given minute volume the oxygen consumption of the heart was greater per beat but less per minute at slow than at fast pulse rates   Similar findings were reported by Starling and Visscher (1922) The reason for the greater efficiency of the heart at slow pulse rates is clear, for with each beat a part of the energy is expended in raising the intraventricular tension sufficiently to open the semilunar valves and only after this has been done can expulsion of blood take place At slow pulse rates that expenditure of energy is relatively less and a relatively great amount of the total energy spent is used for the purpose of propelling blood

The important principle which has developed from the work on the heart-lung preparation is this *changes in the condition of the cardiac muscle are reflected in alterations of the amount of energy expended by the heart to accomplish a given task rather than in variations of the actual work accomplished*

Fatigue of the heart in relation to heart failure   According to the Starling school, fatigue is the opposite of tone, which is synonymous with "fitness "   This idea of tone is rather different from that advanced by Gaskell (1880), who used the word to mean resistance to filling in diastole, or varying distensibility of the ventricles   Starling and his coworkers stated on the other hand. "It is evident from what we have said that the word "tone" is properly employed as synonymous with the physical condition or fitness of the muscle fiber and its measure is the energy set free per unit length of muscle fiber at each contraction of the heart "   According to this concept tone is more nearly concerned with the degree of emptying than with the degree of filling Hence, fatigue means that for a given filling (diastolic volume) the emptying is less complete than when the heart is "fresh" (i e , when the tone of the heart is good)   A fatigued heart can maintain a given output but only provided the degree of filling, and consequently the residual blood, is increased   Therefore, a fatigued heart must dilate in order to maintain the same minute volume   This point is such an

important one in the understanding of cardiac failure that we may do well to quote Starling's words "A heart in good condition, i e , one with a good tone, will carry on a large circulation against a high arterial pressure and nearly empty itself at each contraction, while a heart with a defective tone, as in the case when it is tired, can carry on the same circulation, but only when its fibers at the beginning of each contraction are much longer, i e , when the heart is dilated In the latter case the output of blood will be the same as in the former, but both the systolic and the diastolic volumes of the heart will be increased "

From the quotations which have just been made it is evident that Starling regarded cardiac fatigue as being manifested in the first place by dilatation of increasing degree, the cardiac output remaining constant The investigations which have been quoted on the cardiac output in persons with cardiac failure are in general agreement with this conclusion, for it was shown that in such individuals there is not necessarily any change in the minute volume of the heart

It is well known that an increase in venous pressure almost always accompanies advanced congestive heart failure, and it has been shown [Schott (1912)] [Harrison, Harrison, Calhoun and Marsh (1932)] that patients with this disorder exhibit on exertion a rise in venous pressure which is abnormally great and unusually prolonged after the cessation of exercise In this regard the experiments of Socin (1915) are of interest This author showed that after experimental chloroform poisoning, a greater rise in venous pressure is necessary in order to cause a given increase in cardiac output than under normal conditions The state of affairs is then similar in the experimentally fatigued heart, the experimentally poisoned heart, and the patient with congestive heart failure The common physiological change in these conditions is not an alteration in the output but a change in the relationship of the output to the venous pressure In such conditions the heart may pump a normal amount of blood but it only does so, with a higher venous pressure, at the expense of a greater diastolic volume, and with a greater expenditure of energy As has been shown in the preceding sections, it is this elevation in venous pressure which is responsible for the chief clinical phenomena of congestive failure

If the conclusions of the preceding paragraph are correct, then heart failure (fatigue) is a question not of insufficiency but of inefficiency

An inefficient machine is one which converts a relatively small amount of its expended energy into mechanical work

Rohde (1910) found that injury to the heart increases its oxygen consumption and the researches of Starling and Visscher (1922) and of Hemmingway and Fee (1927) showed the oxygen consumption, i e, its energy expenditure, to be proportional to the diastolic length, which is to say to the degree of dilatation

In comparison with the normal heart, the fatigued and the dilated heart of the patient with congestive failure has to consume more oxygen in order to pump a given amount of blood against a given resistance   This inefficiency constitutes the cardinal physiological change associated with congestive heart failure

B *Acute experimental heart failure in intact animals*   The applicability to man of conclusions arrived at from the study of the heart-lung preparation has been questioned, because of the artificial conditions involved   It is therefore of interest to know that recent studies on animals subjected to no operative procedure have led to similar findings

Harrison, Friedman and Resnik (1935) devised a technique for determining the mechanical efficiency of the dog's heart without exposing the animal to operative procedures   The work of the heart was determined by measuring the cardiac output and the blood pressure   The oxygen used by the heart was estimated from measurements of the coronary blood flow and the oxygen content of arterial blood and of the blood escaping from the coronary sinus, which was cannulated through the external jugular vein without opening the chest   Heart failure was produced by the administration either of chloroform or of potassium chloride   It was found that the former drug usually produced left-sided failure with pulmonary edema, while potassium chloride tended to cause right-sided heart failure associated with rise in the systemic venous pressure   The mechanical efficiency of the heart which was calculated by dividing the energy expended—as derived from the oxygen consumption—into the work performed, was found to undergo striking decline as heart failure occurred   In many of the experiments the cardiac output declined, but heart failure in some instances was not associated with significant changes in this function, either considered as such or in relation to the metabolism   These observations led to the following conclusions as regards the mechanism of acute

experimental heart failure in intact animals (1) Diminution in the tissue blood supply is not an essential factor (2) The heart does not fail as a whole but either side may fail independently of the other Severe and fatal heart failure may occur without systemic engorgement (3) As regards the heart itself the essential physiological change is dilatation with an associated decline in the mechanical efficiency of the heart as a pump The conclusions arrived at from the study of the heart-lung preparation are therefore applicable to the intact animal

The final demonstration of the similarity between the mechanism of heart failure as observed in the heart-lung preparation and that seen in patients cannot be made at the present time for it necessarily involves a simultaneous determination of the work done and the energy expended by the heart No method applicable to patients exists for measuring the latter function However, the studies of Starr and his colleagues (1934), which showed that the essential difference between patients with advanced cardiac disease and subjects with normal hearts consisted not so much in the actual work done by the heart but in an increase in size in proportion to the work accomplished, constitute importance evidence in this regard While direct proof is lacking the indirect evidence seems sufficiently strong to justify the conclusion that heart failure in man, like that in the heart-lung preparation and in intact animals receiving drugs which injure the heart, is primarily a matter of progressively diminishing mechanical efficiency as the result of dilatation As regards the tissues the essential alteration is engorgement in either or both of the greater and lesser vascular beds The term "congestive heart failure" is therefore more accurate than the expression "cardiac insufficiency " In so far as the heart itself is concerned the essential alteration is not so much a matter of failure to perform work but rather of performing it only when excess energy is expended The failing heart is inefficient rather than insufficient [2]

[2] The dilated heart may be compared to a motor car which is being driven in second gear The dilatation which occurs in a healthy heart in response to effort is associated with increased efficiency as is the shift to second gear when the engine begins to falter on a steep hill The heart which is dilated as the result of disease is like the motor car which is being driven in second gear over level ground at a rate of forty miles per hour The task is being performed at the price of an excessive expenditure of energy

VII THE RELATION OF CONGESTIVE HEART FAILURE TO ENLARGEMENT OF THE HEART

If one omits from consideration certain cases of pericardial disease in which the filling of the heart is interfered with by fibrosis or by fluid, it is safe to assert that the one constant post-mortem finding in persons dying of congestive heart failure is enlargement   Aside from certain exceptional instances which have already been discussed (page 282), dilatation is present regardless of the duration of the disease, and in subjects with chronic congestive failure hypertrophy of some degree is regularly encountered   It is therefore necessary to relate these two types of cardiac enlargement to the pathogenesis of congestive heart failure

The studies of Starling and his colleagues have shown that slight degrees of dilatation, when due to increased work are associated with increasing mechanical efficiency, but that dilatation brought about by impairment of the muscle is accompanied by progressive decline in the efficiency   Since the heart's power to do more work depends on its ability to dilate and thereby to expend more energy, it is evident that a heart which is already dilated is drawing on its reserve power and has a smaller margin of safety   Such conditions in the heart-lung preparation are analogous to the clinical state of the patient who is asymptomatic at rest but is beginning to have dyspnea on progressively less effort

As his malady progresses the patient with cardiac disease eventually develops symptoms at rest and it has been shown that these symptoms are to be attributed to congestion brought about by an increase in venous pressure, either in the pulmonary circuit, producing dyspnea, or in the systemic channels, producing venous distention and edema This stage of cardiac disease corresponds in general with the second phase of cardiac fatigue in the heart-lung preparation, in which the degree of dilatation necessary to maintain a relatively normal output is associated with a rise in venous pressure   *Congestive heart failure may therefore be defined as a state in which the heart has become so dilated that it has produced a rise in the venous pressure—either systemic or pulmonary*   The greater filling pressure serves the purpose of insuring that, in spite of the myocardial impairment, the filling and hence the output of the heart shall remain at a relatively normal

level As improvement from congestive failure occurs the better condition of the muscle allows it to accomplish as much work, even though driven by a lessened filling pressure

It is probable that dilatation, the immediate response to work, precedes and perhaps causes hypertrophy, which has usually been regarded as a chronic response to a sustained increase in work Some authors have doubted whether overwork actually is the cause of hypertrophy [Christian (1928)], which has sometimes been ascribed to alterations in the nutrition of the heart [Lewis and Drury (1923)] It is true that hypertrophy is sometimes encountered in subjects who have no valvular lesion, no increase in blood pressure and no obvious cause for a general increase in the work of the heart In such cases areas of disease are usually encountered in the heart muscle As regards the individual healthy muscle fiber, it is probably unimportant whether an increased load is encountered because of excessive strain on the heart as a whole or because the diseased fibers are unable to carry on their share In either case the fiber exposed to overwork tends to become thicker In young animals excessive exercise appears to result in hypertrophy [Külbs (1906)] [Steinhaus, Hoyt and Rice (1932)], but in human adults it is probably necessary that the strain be continuous Such a conception accounts for the fact that athletes and laborers do not have hypertrophied hearts, while patients with valvular lesions usually do That hypertension uncomplicated by myocardial disease can produce hypertrophy is shown by the experiments of Koch (1931), who found hypertrophy of the left ventricle of dogs and rabbits in which an increase in blood pressure had been produced by cutting the aortic and carotid sinus nerves

Hypertrophy offers a mechanical advantage because the thicker fiber is more powerful However, it carries with it a potential chemical disadvantage which becomes actual once a certain degree of hypertrophy has been exceeded

Hypertrophy and tachycardia in relation to myocardial fatigue An important relationship exists between the rate of the heart and its tendency to become fatigued The harmful effects of tachycardia can probably be best illustrated by those clinical instances in which young individuals with otherwise healthy hearts develop congestive failure during prolonged bouts of paroxysmal tachycardia Such

ndicate that even a normal human heart becomes fatigued at
vely rapid rates   One factor which probably plays a rôle
trated by the experiments of Evans and Matsuoka (1915),
und that for a given minute volume and peripheral resistance
ygen consumption of the heart per unit of time was greater
d than at slow pulse rates   Hence tachycardia makes the heart
icient   A second important factor is the diminution of blood
 to the left ventricle under these conditions   The coronary
> this chamber is intermittent and takes place only during
e, for during systole the pressure in the left ventricle, being
· than that in the coronary artery, effectively shuts off the
ry flow   The duration of systole is relatively independent of
art rate and hence the total duration of systole per minute is
: and that of diastole correspondingly less during tachycardia
cardia thus increases the need for oxygen but at the same time
res with its supply to the heart

siderations such as these may be of some importance in explain-
e harmful effects of tachycardia   However, the factors men-
 cannot be the sole ones, because some animals such as the rat
e guinea pig normally have resting heart rates of two hundred
ee hundred or more, which is faster than the maximum rate
 can be tolerated by man and other large animals   It is clear
: the heart muscle is not to become fatigued the duration of
le must be sufficiently long to allow the heart to recover com-
· between beats and it is therefore evident that in animals which
lly have rapid hearts the recovery process can take place more
y than in other animals which are unable to tolerate prolonged
rates   The investigations of physiologists have demonstrated
he recovery process in muscle is complex but that the oxygen
· to the heart muscle is probably the single most important
 involved   Is there any reason why it should require a longer
or oxygenation of the heart muscle to take place in the larger
ls than in the small ones?
rder to study this question Harrison, Ashman and Larsen (1932)
observations on the relationship between the heart rate and the
less of the cardiac muscle fibers of rats, guinea pigs, rabbits,
sheep and cows   Similar data were obtained from the hearts of

persons who at autopsy showed no evidence of cardiac disease, and from patients who died of congestive heart failure. It was found that the average heart rates varied from sixty in the cow to 340 in the rat while the mean fiber thickness ranged between eleven and eighteen micra in the normal animals, the thickest fibers occurring in those with the slowest pulse rates and vice versa. The relationship between the heart rate and the fiber thickness was similar in human subjects without heart disease to that found in the animals. However, the patients dying with cardiac failure had much thicker fibers than any of the normal animals, but their pulse rates were not correspondingly smaller.

The recovery process in the heart muscle must take place during diastole because it is obvious that a muscle cannot contract and recover from contraction at the same time. It is highly improbable that oxygen can diffuse into the muscle fibers during systole because the capillaries of the heart, or at least those of the left ventricle, are empty of blood during the time when pressure in the wall of the heart is greater than that in the aorta. Hence, it is likely that the duration of diastole represents the time during which oxygen diffusion may take place into the cardiac muscle. According to A. V. Hill (1929) the rate of diffusion of oxygen through tissue varies as the square of the distance diffused. When the values obtained by Harrison, Ashman and Larsen for the cardiac fiber thickness were squared and plotted against the duration of diastole in animals of the various species a curve was obtained in which all of the points for the normal hearts, including those of man, fell reasonably close to a straight line. The points for the persons dying of cardiac disease fell far above this line, indicating that the duration of diastole was too short in relation to the fiber thickness.

One can consider one half of the muscle fiber as being supplied with oxygen from the capillaries on the corresponding side and the opposite half from the capillaries on its side. The greatest diffusion distance is therefore one-half the thickness of the fiber and the mean diffusion distance is one-fourth the thickness of the fiber. If the fiber thickness is doubled the mean diffusion distance is doubled. However, the mean head of pressure (the average oxygen tension of the blood in the capillaries) is not doubled but remains the same. As oxygen diffuses

the head of pressure diminishes and hence it diffuses more rapidly
through the outermost than through the central portion of the fiber
Therefore, since the time required for complete recovery to take place
after the contraction is dependent on the time required for oxygen
to reach all portions of the fiber, one would expect that an increase of
two-fold in fiber thickness would more than double the recovery
period   From such reasoning one arrives at the conclusion that the
thicker the muscle fiber the slower the heart rate should be, not only
actually but also relatively   The mean fiber thicknesses found by
Harrison, Ashman and Larsen were 16 2 and 31 8 micra, respectively,
for the normal adult hearts and for the hearts of patients dying with
congestive failure   Now the average length of diastole, as deter-
mined in a group of persons without cardiac disease, was 0 56 second,
and it is reasonable to believe that this value represents approximately
the optimal duration of diastole   If, as A V Hill calculated, and as
is indicated by our studies of hearts from the various animals, the
duration of diastole varies as the square of the distance through
which oxygen has to diffuse, then it can be readily calculated that the
optimal length of diastole in the patients dying with congestive heart

failure should have been $\dfrac{0\ 56\ \times\ 15\ 9^2}{8\ 1^2} = 2\ 3$ seconds, which corre-

sponds to a heart rate of approximately twenty-three per minute if the
duration of systole is assumed to be 0 3 second   (I do not mean to
imply that such a slow heart rate would be desirable for it would
probably be associated with weakness and possibly with unconscious-
ness   Insofar as the general condition of the patient is concerned,
such a bradycardia might be very harmful, but the calculations appear
to indicate that it would tend to allow for complete recovery of the
cardiac muscle between contractions, and hence to diminish cardiac
fatigue)
   These calculations tell us something about the optimal length of
diastole and by a similar way we may arrive at a rough estimate of
the fastest rate which can be sustained for any considerable length of
time by enlarged hearts   Clinical experience teaches us that even the
normal heart will not tolerate extremely rapid rates for an indefinite
period, and it is probably safe to assume that manifestations of fatigue
will develop in the normal adult human heart if it beats indefinitely

t a rate of more than 150 per minute   At such rapid rates the duration of systole is somewhat diminished, if we assume it to be 0 2 second, then the duration of diastole will be $(60/150) - 0\ 2 = 0\ 2$ second   Now from calculations like the ones in the preceding paragraph it can be shown that in patients with congestive failure fatigue will become manifest at a diastolic duration of $\dfrac{0\ 2 \times 15\ 9^2}{8\ 1^2} = 0\ 76$ second, which corresponds to a heart rate of about fifty-seven beats per minute

On theoretical grounds then one would expect that the patient who has marked cardiac hypertrophy will tend to develop cardiac fatigue, even at the normal "basal" rate, as thicker muscle fibers require a longer rest period in order to recover between beats, and when this is not forthcoming, recovery may be incomplete and fatigue result

The question at hand may be approached from another angle Krogh (1929) has calculated the tension difference necessary to cause oxygen diffusion between two points   Space does not permit us to reproduce his formula and go through the various steps of the calculation which shows that the oxygen tension required to supply oxygen to the hypertrophic hearts of persons with advanced cardiac disease is more than ten times as much as the tension necessary to supply oxygen to the normal cardiac muscle fiber   By this method of calculation we arrive at the same principle as before, namely, that the physical laws governing oxygen diffusion are such that a thicker cardiac muscle fiber needs a very much longer period of recovery than does a muscle fiber of normal dimensions   The obvious conclusion is that if the hypertrophied cardiac muscle fiber is to maintain a healthy metabolic and nutritional status the heart rate should be slower than the normal heart rate

An attempt to apply mathematics to a complex biological problem is likely to be misleading, and I am aware of the numerous sources of error which may invalidate the quantitative accuracy of the results so obtained   However, the general principles which they illustrate seem to be sound and if they are we have arrived at a reasonable explanation for the curious paradox that a powerful looking hypertrophied heart muscle which shows little or no evidence of disease either on gross or microscopic examination, may yet fail to carry

on an efficient circulation. Hypertrophy of the heart is a compensatory process, but it carries with it a disadvantage, for even when of slight degree it predisposes the heart to fatigue dependent on insufficient oxygenation of the muscle fibers at heart rates which can be tolerated with ease by the unhypertrophied organ, and when it is of extreme degree fatigue may develop even at a relatively slow normal rate

Hypertrophy and dilatation of the heart are processes of such fundamental importance in relation to congestive failure that it may be well before concluding our consideration of them to summarize briefly the main points of the preceding discussion   Both of these processes are originally compensatory adjustments to an increase of the work of the heart in proportion to its strength   Dilatation, by which we mean an increase in the length of the fibers relative to their width, is the immediate response and it offers a chemical advantage because of the greater surface and consequent increased opportunity for chemical interchange between the blood and the fibers   But dilatation puts the heart at a mechanical disadvantage because it increases the energy expenditure for a given amount of work   By some means, as yet unknown, this disproportion between the length and the diameter of the muscle fibers which has been produced by dilatation is followed by hypertrophy, i e , by increase in the width of the fibers and thereby the original relation of length to diameter tends to be restored   However, conditions are not the same as they were in the beginning, because the mass of tissue to be nourished has increased as the square of the radius of the fiber while the surface of the fibers through which the nutritive process must take place has only increased as the first power of the radius   The hypertrophic muscle fiber, while offering a mechanical advantage, suffers from a chemical disadvantage and its tendency will be to dilate further whenever conditions of stress arise   The vicious circle thus inaugurated from processes which were originally benign and compensatory adjustments tends eventually to produce congestive heart failure with its train of untoward phenomena

VIII THE PRINCIPLES OF THERAPY

As has been mentioned, procedures which produce benefit in patients with congestive heart failure may cause an increase, a decrease, or

no change in the output of the heart   At first sight it may seem surprising that two different methods of treatment may each produce improvement and yet apparently exert opposite physiological effects There are however certain considerations which tend to resolve this apparent paradox

If instead of considering the differences one looks for similarities between the effects of the severally useful therapeutic methods, it would appear that their one constant effect is a diminution in the size of the heart   [This has not been demonstrated for all of the therapeutic measures but has been shown for digitalis [Stewart and Cohn (1932)], and for venesection [Gordon (1925)]   The difficulty of detecting slight or even moderate changes in the size of the heart has been discussed   Since it has been clearly shown in the heart-lung preparation, in which ventricular volume can be accurately measured, that the development and the disappearance of heart failure is accompanied by corresponding changes in volume, it appears likely that improvement is necessarily associated in patients with a decrease in the size of the heart]   Diminished dilatation signifies decreased energy expenditure [Starling (1918)]   This may be brought about either through a diminution in the work of the heart, its efficiency remaining constant, through increasing efficiency, the work being unchanged, or by a combination of these effects

Certain procedures such as rest, venesection, the administration of morphine, and total thyroidectomy do not apparently effect the heart directly but produce benefit by decreasing its output and hence its work [Resnik, Friedman and Harrison (1934)]   Other procedures, such as the use of digitalis, have no constant effect on the work of the heart but seem to produce benefit by increasing the efficiency of the myocardium and enabling it to carry a given load with a smaller expenditure of energy   (Such an effect has been demonstrated in the heart-lung preparation by Bodo (1928), and probably occurs in man, although it cannot be demonstrated by methods now available) In properly selected patients quinidine administration appears not only to increase the efficiency by slowing the rate and eliminating the pulse deficit, but also to increase the output and hence the work   If however the effect on the former function is greater than that on the latter the net result will again be a decrease in energy expenditure

The effect of diuretics is chiefly on the extra-cardiac tissues rather than on the heart, but there is some evidence [Friedman, Resnik, Calhoun and Harrison (1935)] which suggests that they also may tend to increase the efficiency of the heart and to diminish the energy expended.

These considerations suffice to explain why a drug like digitalis[3] may decrease the output in one patient, increase it in another and produce benefit in both of them, and why both quinidine and morphine may be useful therapeutic procedures, although having opposite effects on the cardiac output As the evidence accumulates one general guiding principle emerges in cardiac as in other diseases those procedures are useful which tend to diminish energy expenditure and to rest an overstrained organ

IX THE MECHANISM OF HEART FAILURE IN PATIENTS WITH
OBLITERATIVE PERICARDITIS

There is one rather uncommon type of chronic cardiac disease which merits special consideration because it differs fundamentally in several important respects from the more usual types In patients with concretio cordis (obliterative pericarditis), a condition which has been especially studied by Burwell and his colleagues (1932) (1935), the fundamental difficulty consists in an inability of the heart to fill because of the dense fibrous tissue surrounding it In this condition congestive phenomena may be marked, even though the heart is small (In long standing cases the myocardium may undergo marked atrophy) Such patients present not only the manifestations of back pressure, i e , of congestive heart failure, but also those of forward failure The pulse is rapid, feeble and paradoxical, the pulse pressure

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[3] The action of digitalis on the heart is to decrease its size and to increase its reserve In the presence of a high venous pressure such a change in the state of the myocardium may produce an increase in the cardiac output [Cohn and Steele (1932)] On the other hand the peripheral action of the drug causes a decrease in venous pressure [Dock and Tainter (1930)] [Rytand (1933)], and this tends to diminish the output of the heart In normal subjects the latter effect predominates, in patients with congestive heart failure either the peripheral or the cardiac action may predominate and changes in the cardiac output in either direction may occur However, the decrease in heart size occurs regularly [Stewart and Cohn (1932)] and this is, in all probability, accompanied by a diminution in the amount of energy expended by the heart and hence by an increase in mechanical efficiency

low, the heart sounds distant, and the cardiac excursion as seen wi
the fluoroscope is minimal or absent   Such patients are not ben
fited by the usual therapeutic measures and may even be made wor
by digitalis as was shown by Burwell and Strayhorn (1932)   In th
disease, as well as in persons with large amounts of fluid in the pe
cardium, one is not dealing with a fatigued heart muscle but with
myocardium which is capable of expending energy but unable to
so because its ability to dilate has been interfered with by the m
chanical obstruction   The cardiac output, which is low in such cas
increases following operation with resection of the pericardium [Resn
Friedman and Harrison (1934)]   The study of this disorder h
proven fruitful in the general interpretation of the dynamics of hea
failure, for one has been able to observe in the same patient and
the same time, the clinical phenomena of chronic collapse due to fo
ward failure, and the congestive manifestations due to backwa
failure

X A SUGGESTED CLASSIFICATION OF THE GENERAL CIRCULATORY
DISORDERS

This review has not been concerned with *circulatory* failure
general but rather with one special kind   Interest has been center
on a particular type of *heart* failure—that characterized by congestio
The evidence bearing on its pathogenesis has been considered and h
led to the conclusion that its clinical phenomena are dependent
back pressure   In conclusion it may be of interest to attempt
correlate this with other disorders of the cardiovascular apparatu

If local vascular disturbances, including angina pectoris, are omitt
from consideration, one may divide the general circulatory d
turbances into three main groups, each of which is characterized
a special functional alteration and a particular clinical picture (table
In certain conditions the underlying physiological derangement is
increase in the cardiac output and the most important clinical ma
festations are palpitation, plus an exaggeration of the normal cardi
and peripheral vascular phenomena   In this disorder, which I ha
called the hyperkinetic syndrome, the physical signs elicited over t
heart are often suggestive of mitral valvular disease, whereas, t

TABLE 1

The Important Types of General Circulatory Disturbance

NAME	COMMON SYNONYMS	UNDERLYING PHYSIOLOGICAL DISTURBANCES	CHIEF ETIOLOGIC FACTORS	MOST IMPORTANT CLINICAL MANIFESTATIONS	
				Subjective	Objective
The hyperkinetic syndrome	Overactive heart	Increased cardiac output	Thyrotoxicosis, Anemia, Fever, Cardiac neurosis, Pregnancy	Palpitation	Loud heart sounds, systolic murmurs, bounding pulse
The hypokinetic syndrome	Shock, collapse	Decreased cardiac output	Hemorrhage, Trauma, Emotion, Reflex disturbances, Sudden heart failure	Weakness	Diminished blood pressure, feeble pulse
The dyskinetic syndrome	Congestive heart failure, Cardiac decompensation, Cardiac insufficiency	Diminished cardiac efficiency (increased energy expenditure in proportion to work done)	Hypertension, Arteriosclerosis, Rheumatic fever, Syphilis	Dyspnea	Cardiac enlargement, venous distention, edema

The opposite condition is characterized by clinical manifestations due to a diminished blood supply to the tissues   Here the chief subjective phenomenon is weakness and the objective signs are those of diminished circulatory activity   The hypokinetic syndrome is usually of peripheral origin but may be dependent on sudden cardiac weakness

The third type of general circulatory disturbance is congestive heart failure   Here the heart is primarily concerned, and the essential physiological disturbance is dilatation of the cardiac cavities associated with an increased energy expenditure by the heart   This disturbance, which involves efficiency rather than performance, is characterized by the term "dyskinetic"—indicating disordered or labored motion

Failure of the circulation may be either hypokinetic or dyskinetic, or the two may exist in combination (table 2)   Peripheral circulatory failure is always of the former type, cardiac failure may be of either type   Forward failure of the heart produces a hypokinetic syndrome, backward (congestive) failure causes the dyskinetic syndrome   The two types of heart failure may—and often do—exist simultaneously (hypo-dyskinetic syndrome—table 2)

In the hundred years which have passed since James Hope published his book, many important contributions to the subject of heart disease have been made   During the present century particularly, the rapid growth of knowledge concerning etiology, arrhythmias, disorders of conduction, and other important aspects of cardiac disorders, has perhaps tended to obscure a clear point of view concerning the central problem—heart failure   If one attempts to adopt an historical perspective and to select from the numerous valuable contributions to the understanding of the pathogenesis of congestive heart failure, those which will eventually be regarded as of first importance, he cannot overlook these   (1) William Stokes' emphasis on the importance of the state of the heart muscle, (2) Sir James Mackenzie's insistence on the response to effort as the guide to the functional state of the heart, (3) Francis W Peabody's clinical observations, which laid the groundwork for a correct understanding of dyspnea   But the highest homage must be granted to James Hope, whose clinical and pathologic observations led to the formulation of the

TABLE 2

Circulatory Failure

	UNDERLYING PHYSIOLOGICAL DISTURBANCE	CHIEF CLINICAL PHENOMENA		TYPES	EXAMPLES	SITE OF INITIAL DISTURBANCE	
		Subjective	Objective				
I Hypokinetic syndrome (acute circulatory failure)	Diminished blood supply to tissues	Weakness	Feeble pulse, low blood pressure	Hematogenic / Neurogenic / Vasogenic	Hemorrhage / Trauma / Syncope / Nitrite poisoning	Blood / Nervous system / Arteries	Peripheral circulatory failure
				Cardiogenic	Paroxysmal tachycardia	Heart	Forward failure
II Dyskinetic syndrome (congestive heart failure)	Diminished mechanical efficiency of heart. Increased energy expenditure	Dyspnea / Edema	Diminished vital capacity, rales / Venous distention, enlargement of liver	Left sided failure / Right sided failure	Cardiac asthma / Congenital lesions	Heart	Backward failure
III Hypo-dyskinetic syndrome (combination of I and II)	Dilatation (inefficiency) plus diminished output (insufficiency)	Combination of the signs of collapse with those of congestion		Myocardial (diminished emptying) / Pericardial (diminished filling)	Coronary thrombosis / Pericardial effusion Concretio Cordis	Heart	Forward and backward failure simultaneously

Forward failure / Backward failure / Forward and backward failure simultaneously } Heart failure

back-pressure theory, which after one hundred years seems now to be substantiated, and to Ernest H Starling, whose fundamental investigations furnished the physiological basis for a rational understanding of heart failure

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HEAT CRAMPS

JOHN H TALBOTT, M D

(From the Fatigue Laboratory, Harvard University, and the Massachusetts General Hospital, Boston, and the Youngstown Hospital Association, Youngstown, Ohio)

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I HISTORICAL

It has been known for more than 2,000 years that a high external temperature may exert a deleterious effect upon the human body In Jonah IV, 8, there is a reference to a probable victim of heatstroke "And it came to pass, when the sun did rise, that God prepared a vehement east wind, and the sun beat upon the head of Jonah, that he fainted, and wished in himself to die and said 'it is better for me to die than to live'" In Isaiah XLIX, 10, and Psalms CXXI, 6, there is a caution against the danger of being smitten by the sun   In recent medical literature the ill effects of heat have been described for about two centuries

The failure of the human body to cope with a high environmental temperature is generally associated with the clinical conditions that are identified as sunstroke, heat stroke and heat exhaustion   There is another malady less well known, but nevertheless definite in its characteristics, that is associated with extreme external heat and muscular activity   This malady is known as heat cramps   Heat cramps are not uncommon in certain endemic centers although they are relatively unknown to most physicians   There are several reasons for the lack of their general recognition   They are essentially an occupational disease and the majority of patients with cramps are seen by the various industrial surgeons   Secondly, their appearance is associated with definite geographic and climatic locations   Finally, the disease has a low morbidity rate, hospitalization is necessary for only a small percentage of the total afflicted, and the mortality rate of these is low

One of the earliest reports in the literature of heat cramps was issued from the gold mines in Virginia City, Nevada and was published

in 1878 (1)   No name was assigned to this malady described at that time, but the occurrence of severe muscle cramps in miners who worked in an environment with temperatures as high as 120° to 130°F is characteristic of the disease under discussion   The next year cramps were mentioned by name in the excellent monograph by Jacubasch, *"Sonnenstich und Hitzschlag"* (2)   In the chapter on the symptoms of heat stroke, Jacubasch refers to cramps in the extremities among the soldiers in the army of Frederick the Great following long marches in hot weather   In 1883 the United States Geological Survey published a monograph on the Comstock Lode (3) and described in detail the muscle cramps in the extremities of the Nevada miners working at temperatures as high as 157°F.   Five years later Hine (4) discussed the occurrence of cramps in the legs following excessive muscular exertion with profuse sweating in individuals who usually led a sedentary existence   Of special interest in this paper were the author's comments on a possible factor of adaptation with regard to susceptibility to cramps   Church (5), Coplin (6), and Meyers (7) were other observers of heat cramps in the last quarter of the 19th century.

At the beginning of the present century, the rapid growth of various industries in this country was accompanied by a rapid increase in the regional incidence of this disease   In the iron and steel mills this was especially so, and the number of men with heat cramps who were observed each summer in these trades reached an alarming sum Previous to this time, little was known of the pathogenesis of heat cramps, the treatment of them was purely symptomatic, and the methodical investigation of the disease as a clinical entity was just beginning   One of the pioneers in this earlier work was Edsall (8), (9) and to him we owe our first knowledge of the pathologic physiology of this disease   In the Pittsburgh steel district, Edsall had the opportunity to observe many patients suffering from cramps and to study a few of those patients who were acutely ill   Two significant findings made by him in his investigations (10) were the diminished excretion of chloride and the increased excretion of nitrogen in the urine from patients after the onset of cramps

At this same time, men engaged in other occupations frequently reported off duty because of severe cramps in their arms and legs The stoking of furnaces on ships, either commercial or naval, was

such an occupation and there are several reports in the naval bulletins of this apparently new disease affecting the firemen   Elliot (11) observed several patients among the stokers on the vessels of the United States Navy during the forced runs in tropical waters   He offered no suggestion to explain the pathogenesis of these cramps, but it is interesting to note that he employed, among other remedies, saline solution for their treatment   No claims were advanced by him for any specific preventive or curative benefit from the use of saline solution   Fifteen years later Haldane and Moss (12), (13) confirmed Edsall's observation of the diminished amount of chloride excreted in the urine of patients who had cramps and advanced the hypothesis of 'water poisoning' as the principal etiologic mechanism   Recently Talbott and Michelsen (14) have reported five cases of heat cramps observed among the workmen during the building of Boulder Dam It was shown in their study that the significant chemical changes in the serum were the diminished concentration of fixed base and chloride and the increased concentration of protein   It was further shown by them that rather than an excess of water in the blood as postulated by Haldane, the conditions usually associated with anhydremia were present

II DEFINITION

Various descriptive terms have been applied to this morbid process Miner's cramps (12), stoker's cramps (7), mill cramps, cane cutter's cramps (15), and firemen's cramps (16) associate the disease with its occupational occurrence rather than with the nature of the causative mechanism   The general term, muscle cramps, has been used but this includes nocturnal cramps, ischemic cramps and other types in which heat is not an important factor in their pathogenesis   "Heat cramps" has been assigned as a name to this specific malady, it is a good appelation and will be retained in this discussion   The term heat cramps, then, is meant to apply to painful spasms of the voluntary musculature following muscular activity in a high environmental temperature   Since the recognition of heat cramps as a disease entity is recent, this term is listed neither in the United States Navy System of Nomenclature (17) nor in the Standard Nomenclature of Disease (18)

III INCIDENCE

Heat cramps are relatively common in the summer months in certain endemic centers although accurate statistics of their incidence are lacking   There are several causes for the sparseness of data of the incidence of this malady   Many of the patients do not need to be hospitalized and they seek medical advice only when their cramps become severe, knowing full well that mild cramps subside spontaneously   In this respect, the common cold offers a satisfactory analogy.   Another reason for the relative absence of data has been the failure in the past to consider heat cramps as a disease entity to be differentiated from heat stroke and heat prostration and to require a separate listing for each of them   In most instances when cramps have been reported they have been considered a symptom of heat stroke, although there are a few exceptions to this statement   In the United States Navy, Phelps (19) reported 82 cases of heat stroke and 105 cases of heat cramps in the years 1924 and 1925   Our observations at Boulder City and Youngstown[1] confirm this relative incidence   From 1928 through 1933 there were admitted to the Youngstown Hospital 117 patients with cramps and 118 patients with heat stroke, and in the summer of 1934, 49 patients were admitted with cramps and 42 patients with heat stroke   It may be assumed, as an approximation, that in the heavy industries the ratio of heat cramps to heat stroke is about 1:1   A reconsideration of the statistics for heat stroke with these available data gives a better index than heretofore of the incidence of cramps   Thus, in the British Army during the decade following 1901 (20), there were 2,300 subjects hospitalized because of the ill effects of heat   It may be tentatively assumed that approximately half of this number had heat cramps

[1] In 1932 the author studied five cases of heat cramps and two cases of heat prostration in Boulder City, Nevada   In that place the studies were only approximate with regard to intake of food and salt   In 1934, 32 cases of heat cramps and 34 cases of heat prostration were studied in Youngstown, Ohio, through the courtesy of the Youngstown Hospital Association   At that time an adequate metabolic ward was established and all patients were studied while on a strict metabolic regime   In the protocols are given brief clinical reports of 3 patients suffering from heat cramps   These 3 patients were selected as rather typical examples of workmen with mild, moderate, and severe cramps, respectively, among those observed in Youngstown   In tables I, II, and IV are given the observations of the balance data of the urine and blood obtained from these patients

In this country at the present time, the steel industry has probably the greatest annual number of patients suffering from cramps   This is a function of the large number of men employed in these mills, the location of many of the mills in regions that have very hot summers, and the high temperatures at which the men work   Bock (21) found in Youngstown that most of the men employed at the hottest jobs had mild or severe cramps at least once a summer   Probably all of the men who have been employed for more than a decade at the hot jobs in the steel mills have experienced at least one attack of cramps

The prevalence of heat cramps in other countries is quite interesting Heat cramps are observed among the workmen in the coal mines in England (12), in the gold mines in South Africa (22), and in the sugar cane fields in Australia (15)   In the Russian industries they have been recognized and reported in recent years (23)   There is only one discussion of heat cramps by French physicians (24), and they are rarely observed in Germany at the present time, if we are to judge from the German literature on the subject   Weyl (25) makes no mention of cramps in his discussion of occupational diseases   Recently, Noack (26) in reviewing the effect of high temperature on workmen, merely mentions the condition   The probable explanation for this is the rarity of the disease in Germany rather than the failure of recognition

It may be concluded that the incidence of heat cramps is high in the heavy industries where a high working temperature is customary and in certain other occupations in temperate and tropical climates that require strenuous muscular activity

IV MORTALITY

There are no known mortality statistics for heat cramps   The uncomplicated disease is frequently fatal (10), (11), (27), but the mortality rate is a function of many variables that have not been systematically studied in the past

V METEOROLOGICAL CONDITIONS

a A high working *temperature* associated with a high atmospheric temperature are important factors in the production of cramps   In some occupations such as the building of Boulder Dam and serving

in army posts in the tropics, the working temperature is approximately the same as the atmospheric temperature   In other occupations, a high working temperature may be continual and the elevation of the atmospheric temperature may be periodic, the stoking of furnaces on ships and the mining of coal are examples of the latter If heat cramps are a function of the working temperature only, there should be in these occupations no seasonal or periodic incidence This has not been found to be the case and a seasonal variation of the incidence of cramps in temperate climates has been known for sometime   In the Youngstown steel district from 1929 through 1934 more than 90 per cent of the hospitalized patients were admitted between April and October of each year   Similar observations were reported from the Witwatersrand mines of South Africa (22)   The seasonal variation in the deep level atmospheres in these mines may be no more than three degrees Fahrenheit, yet the majority of patients suffering from the ill effects of heat are stricken in the summer months

The temperature at which heat cramps may occur is generally over 100°F   At Boulder Dam (14) where the atmospheric temperatures were essentially the same as the working temperatures, the men had cramps on days when the maximum temperature was 110°F   or above   In the sugar refineries when the men reported off duty because of cramps, Coplin (6) observed the working temperatures to be between 112° and 135°F   Phelps (19) observed no cramps among the stokers on the S S "Wyoming" when the outside temperature remained below 84°F   and the fireroom temperature below 112°F When the outside temperature rose to 90°F   and the fireroom temperature to 125°F , several men reported off duty because of cramps Still higher working temperatures are given by Clendening (27) who observed 150°F. in pullman dining cars   At this temperature some of the chefs had heat cramps   Probably the highest working temperature for any large group of men is found in the steel mills Cameron (28) observed temperatures as high as 3,000°F   only a short distance from the workmen   In many mills the steel floors are sufficiently hot to burn the thin soles of a pair of shoes or to cook a steak in a very short time   It is interesting to note, therefore, that with such a high mean working temperature throughout the year, most of the cramps occur in the summer when the atmospheric temperature is elevated

b Of less importance than the temperature is the *relative humidity*
It is a misbelief that cramps occur only in an atmosphere with a
high relative humidity (29)   It is a fact that most cases are observed
among men working in humid atmospheres   This is because most
hot jobs are associated with a high relative humidity   Conversely,
there are few jobs in excessive heat where the humidity is low   The
building of Boulder Dam is a notable example of the latter condition
In this place the relative humidity varies between 15 per cent and 35
per cent   During the heat waves when the patients with cramps were
admitted to the hospital, the relative humidity at no time exceeded
25 per cent   The wet bulb reading is believed by Haldane to be of
more importance than either the actual temperature or the absolute
percentage of water vapour   He concluded that when the wet bulb
temperature exceeds 78°F continuous hard work becomes impractical
and in an environment with a wet bulb temperature above 88°F it
is impossible for any length of time

In summary, the significant meteorological condition for the produc-
tion of cramps is a high atmospheric temperature superimposed upon
a high working temperature   The percentile relative humidity ap-
pears to be of less importance

VI PREDISPOSING FACTORS

a *Organic disease* and *ill health* increase the susceptibility of the
human body to sudden changes in temperature   This is especially
evident in large cities during the summer heat waves (30)   Many
of the victims of the heat are known to have an organic malady that
probably contributes to their breakdown with the excessive summer
temperatures   In the various industries, quite the reverse is true of
men who succumb to heat cramps   The men exposed to conditions
favorable for the production of heat cramps have strenuous work to
perform that would be impossible in the presence of an existing organic
disease   The one exception to this statement in our experience was a
patient with early Addison's disease   This case was interesting
because the chemical changes in adrenal insufficiency (31) are similar
to those in heat cramps and the preexistence of this disease un-
doubtedly increased the susceptibility to cramps   The blood Wasser-
mann reaction was negative in all of our patients with cramps

b Alcohol has been accused of increasing the susceptibility to heat cramps since the earlier discussions of this malady. Edsall (10) states "Alcoholism has an exceedingly pronounced effect on increasing the tendency to attacks of cramps and apparently on increasing their severity" A similar view is shared by Morton (32), Fiske (33), Horwitz (34), and Weisenburg (35) In the Youngstown group most of the men that we observed customarily took some alcoholic beverages It was impossible to ascertain the amount consumed daily, but it was probably quite large for many of the men Organic evidence of chronic alcoholism, however, was infrequently observed and only one patient developed Korsakoff's psychosis during his treatment for heat cramps

The belief that alcohol is a predisposing factor for heat cramps is probably a result of the effect produced by acute alcoholic bouts and not by chronic alcoholism Many bouts are accompanied by nausea and vomiting, and little or no food is retained as a consequence With the inadequate ingestion of food, there is generally an inadequate ingestion of the mineral salts normally consumed If, in addition, vomiting and diarrhea are present, the reserve of salt and water in the body may be reduced to a critical level This sequence of events is intimately related to the pathogenesis of the disease that will be considered later Meyers (7) noted the onset of cramps following acute alcoholism as did Talbott (14) in Boulder City In the Youngstown series, seven patients admitted that they had been on an alcoholic debauch on the days or day before the onset of the cramps The patient with the lowest serum chloride concentration on admission had ingested nothing but alcoholic beverages during the previous 36 hours

In the above discussion, reference to alcohol implied the stronger drinks rather than beer Certain advantages may be gained from the consumption of beer in moderate quantities In the industrial section of the Ruhr in Germany where the incidence of heat cramps is presumably low, salted beer is the common beverage, likewise, colliers in the English mines used salted beer for the prevention of cramps Coplin (6) noted a similar consumption with good results among the workers in sugar refineries

c A third predisposing factor is a previous period of *inadequate*

assimilation of food Alcohol may be the contributing cause of such a diminished intake as has been previously mentioned Gastro-intestinal upsets (6) (29), with vomiting or diarrhea in the period before the onset of cramps were admitted by six of our Youngstown patients Less severe disturbances may be associated with little more than a loss of appetite It is significant that six of the men in our study had no appetite for breakfast and three had no appetite for lunch the day of admission None of these men was included in the previously mentioned group complaining of diarrhea or vomiting Constipation has been considered a predisposing factor (14), but this is not supported by our observations nor by those of Pryor (36)

d A recent attack of cramps not adequately treated renders the subject susceptible to a second attack which is usually more severe Three of the men in the group with severe cramps that were studied by us had, the day before admission, cramps that were mild and that did not require medical attention It is a common experience that most men with mild cramps recover sufficiently at home without specific treatment to return to work the next day A portion of these eventually succumb to a severe attack

e Another factor less well defined but hardly open to question is *bad hygiene*, which may include living conditions, badly chosen food, irregular habits, and inadequate rest The necessity for periodic physical examinations and an effective social service system to remove many of these predisposing factors seems obvious

In summary, the important predisposing factors of cramps are ill health, acute alcoholism, inadequate assimilation of food, a recent attack of untreated cramps, and poor general hygiene

VII PAST HISTORY

Most of the men in the steel mills have had cramps and it is not surprising that 27 of the 32 men in the Youngstown series gave such a positive past history Only two of the group with cramps had been previously hospitalized for them The remainder had recovered at home Welsh (37) mentions four men suffering from cramps that had worked in the steel mills more than one summer and all but one had had more than one attack of cramps previously One of his patients was observed in ten different attacks extending over a period of three

years   Brockbank (38) described one patient that had had seven attacks in one year

VIII CLINICAL DESCRIPTION

The picture presented by a patient in a paroxysm of cramps following work in an excessive temperature is characteristic and, once observed, it is not easily forgotten   One of the better clinical descriptions of an attack of cramps is given by Welsh (37)   "Gradually involuntary spasmodic contractions of certain groups of muscles occur   The flexors of the fingers as a rule are affected first, these cramps occur every few minutes   In other cases the smaller muscles will remain unaffected and the larger ones of the arms and legs or even the ones of the abdominal wall develop the condition   Sometimes many muscles or groups of muscles are affected at one and the same time, at other times one muscle after another becomes cramped   If untreated the muscle remains contracted from one to three minutes, when it gradually relaxes   The beginning of the cramp is usually ushered in by a few feeble twitchings of the muscle about to be affected, these occur long enough before the general spasm for the patient to realize a cramp is coming   A cool breeze or a sudden jarring of the bed is often sufficient to throw the affected muscles into contraction There seems to be a predilection, for certain groups of muscles affected in the first attack are likely to be the ones affected in succeeding attacks   As the condition improves, the individual cramps are of shorter duration and further apart   In a well developed case the cramps may occur every two or three minutes, later they may be five or ten minutes apart, and finally a few faint contractions may occur at intervals of a half hour.   The pain during the cramps seems to be severe   I have often seen or had patients tell me that they would rather die than go through another attack   The pupils dilate with each cramp   The pulse as a rule is normal, but in some cases might be slightly accelerated, rarely being over 100   The skin is often clammy, sometimes dry, when perspiration becomes free, the patient improves   The patient seldom vomits even though the abdominal muscles be involved "

a   The examination of the affected muscles may show a varied picture Fibrillary twitchings (9) may be observed that proceed or accompany

the cramps and progress with such rapidity and activity that they suggest a mass of lively snakes under the skin Very gentle palpation of the muscles or sudden pressure may produce a violent contraction of the muscles, following which they become boardlike and painful (39) An attempt at voluntary use of the muscles during the contraction is usually thwarted, although we have seen patients in such severe pain that their muscles were used almost automatically In the severe paroxysms, the stony hardness of the affected muscles is most characteristic The spasms do not yield to deep pressure and violent measures have been tried in the attempt to iron them out with the hope that this will afford relief from the pain (1)

b Physical examination of a patient suffering from cramps is essentially negative except for the myospasm The temperature $p\,r$ is seldom below 98°F or above 100°F The two highest temperatures observed by us on admission were 102 2° and 104°F In both of these patients the temperature was normal four hours later The respiratory rate and pulse rate may be slightly increased All patients except two at Youngstown had a pulse rate between 80 and 105 The tachycardia in these two was of short duration The heart rhythm was normal in all patients with the exception of one who had extrasystoles The blood pressure was slightly elevated in one patient, 180/100, and below average in two others, 95/60, 85/50 All observations were in the normal range the next morning except in one patient who was suffering from Addison's disease in addition to heat cramps

The face may be flushed at the time of admission to the hospital The pupils are neither consistently dilated nor constricted, they react to light and accommodation Examination of the chest reveals nothing abnormal that is related to the attack of cramps The muscles of the abdominal wall are frequently involved When this occurs, slight nausea with occasional vomiting may be present

The extremities, the commonest site of cramps, show no vasomotor changes The deep reflexes may be temporarily exaggerated or depressed (8) The Chvosték and Trousseau signs are always absent Sensation of all qualities is unaffected (38) The mental state in uncomplicated cases is not remarkable In very severe cases the patients may be mentally distracted because of the pain and inflict bodily damage on themselves

c. The *prodromal symptoms* when present are vague and generally escape notice   The attack may be preceded by mild vertigo, headache, or feeble spontaneous twitchings of the muscles   Usually the first symptom is muscle spasm accompanied by severe pain

d The *time of onset* of the cramps varies widely and may be at any time of the day or night   The usual time is after midday and before midnight   Frequently, one or two hours of strenuous hot work by a susceptible individual are sufficient to cause cramps   With other individuals cramps do not appear until the end of the shift   Finally, some men work the entire shift with either mild cramps or none at all only to be seized with violent spasms while in the bathhouse or at home   McCurdy (40) comments on the number of men taken ill after they have taken their showers and started toward their homes In our series the longest interval between the end of work and the onset of cramps was 18 hours

e The *pain* suffered by a victim of generalized cramps is most excruciating and the first medication usually considered after seeing a man with severe cramps is morphine   Cameron (28) stated that he had never seen such agony as these men apparently suffer   The patients with mild and moderate cramps prefer to lie quietly lest any movement incite a paroxysm   Those severely affected move about in bed or may attempt to walk to forget their pain, excruciating as any motion may be for them   On the Boulder Dam project in the summer of 1931 several workmen because of painful cramps were reported to have jumped into the swift Colorado river, where rescue was uncertain   In spite of the severity, the pain subsides simultaneously with the cessation of the cramps   The mechanism of the pain is not known, but symptomatically it is similar to that experienced in nocturnal cramps   Perlow's observation (41), that muscle pain is not produced by a single mechanism but that activity, anoxemia, and circulatory stasis all contribute, may be extended to include a disturbance of the electrolyte distribution

Evidence that the pain originates peripherally in the muscle and not centrally in the nervous system is given by Weisenburg (35)   He studied a forty-year old male cook who had anterior poliomyelitis as a child and was left with paralysis and atrophy of the left leg and loss of reflexes   As an adult, this man had heat cramps which were as

painful and violent in the left leg as in the right   Weisenburg con-
cluded that the origin of the pain was in the muscle

f The *severity* of a paroxysm of cramps may vary within wide
limits   The patients with very mild cramps may have only the mus-
cles of a few fingers involved   Many of the men have cramps so
mild that the spasms do not interfere appreciably with their work
With others the day's work is finished only with difficulty, but medical
attention is not sought   More extensive involvement requires imme-
diate cessation from work   The condition of the severely or critically
ill workmen is recognized immediately and medical attention is
urgent   Such patients usually have generalized, frequently recurring
cramps and need constant supervision   An inverse correlation be-
tween body temperature and severity was noted by Elliot (11)   This
observation was not confirmed in our series

g The *muscles affected* may include most of the voluntary muscles
of the body but usually are confined to those most actively employed
while at work   Various authors have commented upon the absence
of cramps in certain groups of muscles, but where one author failed to
observe cramps in a certain anatomical location, another author was
successful   Cramps have been observed in the muscles of the face,
neck, shoulders, upper and lower arms, hands, back, chest, abdomen,
upper and lower legs, and feet   There seems to be a predisposition for
certain groups of muscles in certain individuals, the group or groups of
muscles affected in the first attack are likely to be the ones affected
in succeeding attacks (37)

There is little evidence that involuntary muscle is ever the site of
heat cramps   Diarrhea, which would probably follow spasm of the
intestinal musculature, is extremely uncommon in patients with
skeletal muscle cramps   Any nausea that is present is very mild and
of short duration   Spasm of the heart muscle is probably very rare,
in fact, it is doubtful if it ever occurs   Only one patient has been
seen by us whose symptoms suggested such a disturbance   This man
was suffering from precordial pain and subsequent examination of his
blood showed changes that are associated with heat cramps   Cramps
of the myocardium was therefore considered a diagnostic possibility
Further proof of changes in the myocardium associated with heat
cramps is lacking   In 1932 Bunn (42) took electrocardiogram tracings

from 15 patients with cramps shortly after they reported off duty No significant changes were observed by him

h. A belief that *sweating ceases* before the onset of cramps or heat stroke is common among men working at hot jobs (1), (43), (44) This is one of the signs closely watched for that promptly causes the men to stop work   The importance of sweating in the causation of cramps makes this phenomenon one of more than casual interest Without presenting experimental evidence, Haldane (45) suggested that marked sweating might be followed by a fatigue of the sweat glands and a secretion of a more concentrated salt solution   Thus an economy of body fluid would be allowed at the expense of a dissipation of body salt   Such a sequence of events if it occurred might produce cramps   Experimentally, fatigue of the sweat glands after prolonged sweating is not proved   Clinically, fatigue of the sweat glands is observed infrequently   Elliot (11) reported three cases of severe cramps and all were sweating profusely while under observation. Our experience is similar   In no instance was sweating absent and in most cases it was abundant   It may be concluded that fatigue of the sweat glands and cessation of sweating is not a regular precursor of heat cramps.   The failure to continue sweating, occasionally observed among subjects exposed to high temperatures, is nevertheless a danger signal and represents a failure of the body to dissipate heat adequately   The recognition of this condition should be followed by the proper medical treatment

i The *reproduction of cramps* by artificial means between spontaneous paroxysms is possible in patients with moderate and severe spasms Counter pressure applied against a flexed affected extremity is usually successful   Direct pressure is less successful   Cold air or cold water (4) are recognized as factors in the production of cramps and may be employed for this purpose   Coplin (6) and others (11) (36), caution against the use of cold baths in severe cases because of a possible recurrence of the cramps   As previously mentioned, workmen often finish their shift and are stricken with cramps during their shower bath   Hot water is less apt to produce cramps than cold (8)   At Youngstown three patients with moderate or severe cramps were put in a hot pack for about 30 minutes   They continued to have cramps during their stay in the pack   A mild alternating current (28) is

another means of reproducing cramps which may be employed experimentally

The importance of producing cramps in a subject who presumably had cramps before admission is twofold   The validity of the diagnosis may rest upon producing cramps after admission   Secondly, the test of the effectiveness of certain therapeutic measures is the inability to produce cramps after treatment   By means of this technique, one patient could be used more than once if the first therapy administered proved to be ineffective

IX   SUSCEPTIBILITY AND ADAPTATION

a   Susceptibility to heat cramps implies that adequate adaptation to hard work in a high environmental temperature has not been gained   An absence of adaptation to heat was first mentioned by Hine (4) in 1888   This phenomenon is generally evident the first days of a heat wave and the incidence of cramps is greatest during these days before adaptation is complete   Meyers (7) did not appreciate that the incidence of cramps was a function of adaptation, but he did observe a high incidence of cramps among the stokers the second day out of port

At Boulder City (14) all of the patients with cramps were admitted the first few days of a heat wave which was generally preceded by a period of cool weather   Similar findings were observed in Youngstown   Consideration of the available data suggests a maximum susceptibility to cramps the first few days of a high temperature period with a decreasing susceptibility as the hot weather continues   This sequence of events is applicable to patients with heat cramps only, and is quite contrary to the admission data for patients with heat prostration   Few patients suffering from heat prostration were admitted concurrently with the heat cramp patients   They were stricken later as the heat wave continued   The incidence of heat cramps early in the heat wave and of heat prostration later suggests different mechanisms as the cause of these apparently related conditions   Without pursuing the differential discussion further, it is suggested that at least one factor is responsible for the production of cramps   This factor is the failure of the body to adapt itself to the rapidly increasing environmental temperature

The importance of adaptation of the workmen to the heat of the Witwatersrand gold mines is discussed by Cluver (22). From his studies on the various disturbances caused by heat among a working population that averaged 200,000 men, he concluded that susceptibility was a function of at least two factors   The tabulation of the tribal distribution of the workmen suggested a greater susceptibility to heat among the natives from the cool, dry areas   This was considered an inherent lack of adaptation   Secondly, he observed a greater susceptibility to heat the first few days on a hot job   This lack of adaptation, which may be considered as acquired susceptibility, is a similar phenomenon to the one observed by us

The incidence of heat cramps in the negro is the only evidence that we have concerning a possible inherent adaptation to high temperatures   It might be argued that the exposure of many generations of these people to high temperatures would have a favorable effect on their resistance to this malady.   This impression is not borne out by the observed facts   In Youngstown the average number of negroes employed in the steel mills is about 10 per cent of the total   Of the 32 cases of heat cramps, 37 per cent were negroes   It was concluded that any inherent adaptation possessed by the negro was insignificant when compared with his lack of acquired adaptation

A predisposition to muscle spasm has been reported by Edsall (8)   In the childhood history of one of his patients, there was a persistent tendency to myospasm   With this predisposition, extreme heat or extreme cold was likely to cause muscle spasm   There was no patient observed by us with such an inherent tendency to muscle spasm, which is not to be confused with susceptibility to heat   There was, however, a history of the frequently observed nocturnal cramps in two of the patients seen in Youngstown   The relation between nocturnal cramps and heat cramps is probably a remote one

b   If the phenomenon of adaptation to high temperatures is accepted as probable, an inquiry regarding the mechanism is then in order.   Acquired adaptation may be related to the sweat glands, to the tissues of the body generally, or to a combination of the two   There are certain data that suggest a specific reaction of the sweat glands in this process   Moss (12) noted that colliers who were apparently acclimated to high temperatures lost about double the quantity

of sweat their unacclimated colleagues did   Vernon and Warner (46)
observed a similar trend in their observations, but did not confirm the
results of Moss quantitatively   They observed in a human subject
an increase in the amount of sweat lost from 530 cc to 630 cc during
four hot room experiments   These observers concluded that adapta-
tion to high temperatures is associated with an increased response of
the sweat glands

Not only does the volume of sweat increase as adaptation progresses,
but simultaneously with this process, there is a diminution in the
concentration of the various constituents in the sweat   Dill (47)
observed a decrease in the concentration of chloride in the sweat
from 18 m Eq to 12 m Eq during a three-day period of acclimatization
at Boulder City   Greater decreases in phosphorus and nitrogen were
noted in one subject   The diminished loss of chloride in the sweat
with a sparing of this substance by the body may prevent depletion
to a dangerous level

Adaptation by the body to repeated losses of sweat was studied by
Talbott (48) in patients undergoing three successive surgical opera-
tions about 10 days apart   The apparent negative chloride balance
for the four-day period after each of the three operations in one patient
was 780,330 and 310 m Eq   It was assumed in this study that the
negative chloride balance represented chiefly chloride lost in the sweat
The conclusion drawn from this study was that there was an adapta-
tion of the sweat glands with an excretion of a more dilute concen-
tration of chloride following the successive surgical procedures

   c   Certain *practical considerations* may be deduced from these studies
of acclimatization   During the first few days of a heat wave, or
during a change from a cool to a hot environment, activity should be
restricted and the salt intake liberal   This should be applied par-
ticularly to workmen beginning a new job   For seasoned workmen
at hot jobs, increased consumption of salt is probably sufficient   The
same precautions should be followed after a cool wave of more than a
few days' duration, as adaptation is rapidly lost   Rigorous measures
were adopted by Cluver (22) in carrying out similar ideas   A proba-
tionary period of two weeks in an especially supervised crew was
required of all recruits   In this crew, over-exercise was prohibited
and the temperatures were not extreme

X CHEMISTRY AND MORPHOLOGY OF THE BLOOD

a Concentration changes in the *protein of the serum* and *hemoglobin of the blood* in heat cramps (tables I and II) are of an order of magnitude infrequently observed in clinical medicine Their altered concentration associated with the attendant dehydration approaches the increase observed by Schmidt (49) in severe cases of cholera The

TABLE I

PATIENT	DATE	OXYGEN CAPACITY	SATURATION	CELL VOLUME	(NON PROTEIN NITROGEN)s	(SUGAR)b	(OSMOTIC PRESSURE)s	RED BLOOD CELLS	WHITE BLOOD CELLS	POLYMORPHONU-CLEAR CELLS	LYMPHOCYTES	(LACTIC ACID)b
Experimental observation on arterial blood from three patients with heat cramps												
	1934	m eq per liter of blood	per cent	per cent	mgm per 100 cc of serum	mgm per 100 cc of blood		mil-lions		per cent	per cent	m eq per liter of blood
M S	June 27	10 00	93 6	49 6	33 5	103		5 16	11,350	77	22	1 5
	June 29	9 15		47 1	33 2	91		4 42	6,100	68	28	
J D	June 1	9 11	93 0	47 6	44 2	129	150	4 89	16,000	93	6	
	June 2			43 3		129	149	4 57	11,300	85	13	
	June 3	7 50	95 5	40 9	28 8	105	145	4 51	7,150	51	41	
D N	July 13	8 94	93 5	45 6	30 1	144		4 90	8,800	67	29	
	July 15	8 65		40 6	31 9	111		4 75	6,300	74	21	
	July 17	8 17	95 0	41 5	27 8	118		4 56	5,800	52	40	
Maximum and minimum observations from thirty-two patients with heat cramps on day of admission												
Maximum		10 55	96 1	55 1	106 0	165	156	6 12	15,100	93	35	2 7
Minimum		8 46	84 0	43 6	30 1	91	143	4 40	8,300	61	6	1 0

highest serum protein determination observed by him was 12 7 grams per cent In the literature on heat cramps Raschewskaja (23) reports a serum protein concentration of 12 6 grams per cent obtained from a patient 24 hours after the onset of cramps The highest concentration observed by us was 10 6 grams per cent Such values are seen clinically in only one disease not associated with dehydration This is multiple myeloma

The decrease in serum protein concentration during hospitalization in patients with cramps in the Youngstown study varied between 0 5 and 5 6 grams per cent   The total protein on admission which is greater than that on discharge is accounted for by the increased concentration of serum globulin   The serum albumin was determined in seven instances where a high total protein was observed and invariably the albumin concentration was below 3 4 grams per cent   In con-

TABLE II

PATIENT	DATE	$(HCO_3)^-$	$(Cl)^-$	$(H_2PO_4)^= + (H_2PO_4)^-$	$(PROTEINATE)^-$	$(Na)^+$	$(K)^+$	$(Ca)^{++}$	$(Mg)^{++}$	Σ CATIONS	Σ ANIONS	pH
		Electrolytes of arterial plasma from three patients with heat cramps										
	1934	*Concentrations are expressed in m eq per liter of serum*										
M S	June 27	27 5	98 6	3 1	20 4	136 6	6 0	6 3	3 9	152 8	149 6	7 44
	June 29	28 3	107 6	1 8	15 7	141 0	5 1	5 0	3 6	154 7	153 4	
J D	June 1	24 0	94 6	4 3	20 4	130 0	6 3	6 0	3 5*	145 8	143 3	7 18
	June 2	24 8	97 8	3 7	18 1	132 8	5 1	5 4	3 5*	146 8	144 4	7 26
	June 3	26 7	104 4	3 0	15 8	139 0	3 4	4 9	3 5	150 8	149 9	7 34
D N	July 13	29 5	88 4	3 0	19 7	130 5	5 1	5 8	3 8	145 2	140 6	7 42
	July 15	27 9	99 6	2 5	15 5	133 0	6 2	5 0	3 8*	148 0	145 5	7 47
	July 17	27 8	100 6	2 0	16 0	136 0	4 8	5 1	3 8*	149 7	146 4	7 43
	Maximum and minimum concentrations observed in thirty two patients with heat cramps on day of admission											
Maximum		29 5	104 0	4 3	24 4	140 0	9 1	7 1	4 5	152 8	150 1	7 44
Minimum		16 9	79 8	2 1	17 7	121 0	3 5	5 1	3 0	136 9	134 6	7 08

* Assume

trast, the serum globulin concentration was increased from 2 5 to 7 4 grams per cent   Neither the absolute level nor the increased concentration of protein was an accurate index of the severity of the cramps   The increase seemed to be principally an index of the degree of anhydremia of the blood   And as this anhydremia subsided, there was a fall in serum protein concentration   This subsiding dehydration of blood was frequently associated with recovery from cramps, but

not invariably   The return toward normal of the serum protein was associated with recovery from cramps only if the serum chloride concentration increased simultaneously   In five patients there was no relief from cramps with decreases in serum protein of 0 2 to 1 0 grams per cent   It may be concluded that the changes in the serum protein concentration in patients with heat cramps may be very great, but these changes are secondary to dehydration and are probably not primarily related to the pathogenesis of the disease

The change in the concentration of hemoglobin corresponds qualitatively to the change in serum protein concentration   In the Youngstown series there was an increase in the oxygen capacity on admission over that obtained on discharge of more than four volumes per cent in six patients   The maximum increase observed in Youngstown was 5 6 volumes per cent and at Boulder City, it was 4 2 volumes per cent In one patient only, in the two series, was there no decrease in oxygen capacity during hospitalization

It has been assumed in the discussion up to the present that the anhydremia is essentially a loss of water from the serum only, with a resulting concentration of serum and hemoglobin from this one process There is, in addition to the serum water loss, a loss of water from the red cells of 1 to 5 per cent   The dehydration of the blood can thus be considered a true loss of *blood* water

The calculation of the theoretical increase in protein and hemoglobin from loss of blood water agrees with the actual observations   Let it be assumed that in a normal sample of blood the cell volume is 40 per cent, the oxygen capacity is 20 volumes per cent, and the serum protein is 7 grams per cent   If, then, the serum protein is increased 28 6 per cent to 9 grams, and the cell protein increased 4 per cent, the cell volume will be increased by 13 per cent   Using the above data $\dfrac{\Delta Vc}{\Delta Ps} = \dfrac{13}{28\ 6} = 45$ The observed ratio calculated from the data on admission and discharge bloods in the Youngstown series agrees well with the theoretical   The average ratio for the mild cases was 40 and for the moderate and severe cases it was 44   Thus the percentile change in serum protein in acute dehydration is approximately twice the percentile change in cell volume   Any description of such marked blood concentration and dehydration of the body is only approximate

(50) because of our inability to include in our measurements the three dimensions

A dilution of the blood by interstitial fluid following exposure to high temperatures or after short periods of muscular effort accompanied by sweating has been observed by several investigators (51), (52)   The dilution of the blood is usually observed within 30 minutes after the beginning of work and is followed in most instances by a concentration   A similar phenomenon of blood dilution was not observed in patients with heat cramps because these patients presumably did not get sick until after the dilution phase   There is one condition related to heat that is observed among subjects exposed to high temperatures that may come on very rapidly during the phase of blood dilution   This condition is heat stroke and patients frequently suc-

TABLE III

Concentration changes in blood during recovery

SEVERITY	NUMBER OF PATIENTS	AVERAGE DECREASE IN SERUM PROTEIN	AVERAGE DECREASE IN RED BLOOD CELLS	AVERAGE DECREASE IN OXYGEN CAPACITY
		grams	*millions*	*vols per cent*
Mild	12	1 39	0 52	1 49
Moderate	13	1 94	0 65	2 62
Severe	5	2 84	0 69	3 26

cumb to this ailment after a very short exposure to a high temperature   The explanation for the rapidity of the onset of symptoms is a withdrawal of fluid from the brain (53) during the blood dilution phase with an ensuing loss of consciousness   Such a phenomenon might conceivably explain the collapse in heat stroke when the chemical studies show very little variation from the normal (54)

The increase in the number of red blood cells on admission above that on discharge parallels closely the increase in hemoglobin Raschewskaja (23) noted a red count of 6 2 million in one patient who had a serum protein concentration of 12 6 grams per cent   May (55) observed red counts of 5 8 and 6 0 million in two patients with cramps In Boulder City the highest count on admission was 6 48 million, a value of 32 per cent over the count on discharge   In Youngstown the highest red blood count observed was 6 12 million, a value of 46

per cent over the discharge count   The average change in concentration of serum protein, red blood cells, and oxygen capacity from the patients in the Youngstown series is given in table III

  b *Blood volume* changes in patients with heat cramps have not been subject to direct observation   If the above assumption that the increase in hemoglobin and protein is associated with a corresponding loss of blood water is correct, then it may be deduced that the circulatory blood volume is appreciably diminished   The absence of medical shock (56) is interesting in connection with an assumed blood volume reduction   These patients, in spite of an increase in serum protein concentration greater than that observed in severe diabetic acidosis (50), did not present the picture of shock frequently seen in the latter condition

  c The *saturation* of arterial blood from 14 of the 32 patients seen in Youngstown was below 94 per cent on admission   The lowest saturation observed was 84 6 per cent   There is no satisfactory explanation for this unsaturation of arterial blood taken half an hour after stopping work   It is interesting to note that in the period from 1928 to 1930 oxygen was given by nasal catheter to many heat cramp patients in the Youngstown Hospital with some apparent benefit   The use of oxygen for the treatment of cramps was empiric and, to our knowledge, no arterial saturation had been determined previously on blood from such patients   In 1922, Morris (57) observed an increased excitability of the neuromyome following anoxemia   It is improbable that the mild anoxemia that was noted by us in some of the patients was an important etiologic agent in the production of the myospasm

  d The *acid-base equilibrium* in the serum

  1 The concentration of electrolytes in the serum from patients with cramps is altered in the mild cases as well as in the severe cases All of the electrolytes except the *bicarbonate* ion show a consistent variation from the normal   The concentration of the bicarbonate ion, however, may be increased, decreased, or normal   The concentration of the bicarbonate ion in the serum from all of the patients in Boulder City was below 24 m Eq   In Youngstown, 20 of the patients on admission had a concentration between 22 and 26 m Eq   In 4 patients it was above 26 m Eq and in 7 it was below 22 m Eq   There

of the CO_2 curve   The level observed in the patients with cramps is apparently variable, depending upon other factors than those intimately associated with the pathogenesis of cramps

Experimental studies on animals exposed to high temperatures have shown a reduction in the concentration of the plasma bicarbonate (58), (59), (60)   In many animals this reduction was associated with a hyperpnoea and a rise in body temperature   Neither of these clinical findings was observed in the patients with cramps

The variation in the arterial pH_s was over the wide range of 7 08 to 7 48   In most patients, the pH_s on admission was below 7 40 This apparent acidosis can be accounted for by a depletion of base rather than an accumulation of determined or undetermined organic acids

2   An increase in the concentration in the serum of *inorganic phosphate* was a constant finding in the patients in Boulder City and was confirmed in Youngstown   An increase in the concentration of this electrolyte in the serum from patients with cramps has not been previously observed   The explanation for this increase is not obvious and consideration of similar changes in analogous conditions offers little aid   An increase of 1 to 3 m Eq may be observed in kidney disease with dehydration and oliguria (61)   In heat cramps dehydration is present, but not oliguria   Addison's disease probably offers a better analogy   In this condition, an increase in serum phosphate has been observed (31) as well as other chemical changes similar to those in cramps   Both adrenal insufficiency and heat cramps are associated with an increased rather than a decreased urinary output   At present we can go little further than to say that a phosphatemia exists in patients with cramps, it is not dependent upon oliguria and there is little evidence that there is a primary disturbance of phosphorus metabolism

3   *Lactic acid* determinations show little variation from the normal (14)   Any excessive lactic acid that might have accumulated during work from physical activity or exposure to heat was probably removed by the tissues before the admission blood was drawn

4 and 5   The changes in the concentration of *chloride and sodium* are consistently present and have been stressed by the author in the interpretation of the mechanism of the production of heat cramps

The lowering of the sodium and the chloride concentration in the body after exposure to high temperature is not a new observation   It was first considered by Weaver in 1897 (62) who suggested a lowering of the body fluid chlorides in patients with heat stroke   He advised treatment of heat stroke by intravenous salt solution   In 1923 Moss and Haldane (12), (13) predicted a lowering of blood chloride as a possible accompaniment of heat cramps   In 1932 Raschewskaja (23) reported a "blood" chloride of 54 m Eq   in a patient with cramps 36 hours after their onset   In 1933 the Boulder City series of five cases were reported   All patients in that group had a serum chloride concentration below 100 m Eq [2]   At Youngstown a minimum of 79 8 m Eq   was noted with only two admission observations above 100 m Eq

Changes in the sodium concentration similar to those of chloride were observed in Youngstown   Of the 32 patients with cramps the minimum serum sodium concentration observed was 121 0 m Eq and the maximum was 140 0 m Eq   A return towards normal of the concentration of sodium and chloride was observed in all patients during recovery   The serum sodium was the only inorganic base whose concentration was decreased in patients suffering from cramps

6 The concentration of *potassium* in the serum was normal or increased 1 to 3 m Eq   Whether or not the concentration of potassium is increased, there is an altered ratio of Na to K as a result of the diminished concentration of sodium   The altered ratio is as frequent an accompaniment of cramps as is the diminution in concentration of the chloride   The significance of this altered ratio has been subject to speculation and it is conceivable that this might be an integral part of the pathogenesis of the disease (23)   That such an explanation is not valid may be concluded from the work of Fenn (63) and from our own observations   Using isolated muscle preparations,

[2] The concentration of chloride is significant only when reported as determined separately on the *serum* or *cells*   A low *blood* chloride means little unless accompanied by a simultaneous cell volume determination   A serum chloride of 102 m Eq and cell chloride of 55 m Eq with a cell volume of 40 per cent gives a whole blood chloride of 83 2 m Eq   This is quite within the normal range of 82 m Eq to 86 m Eq   Let it be assumed that the same chloride concentration is present in serum and cells, but the cell volume is increased to 48 per cent   Then the whole blood chloride as calculated is 79 4 m Eq , an apparently low chloride concentration

Fenn was able to alter muscle irritability by changing the K concentration in the fluid surrounding the muscle. A maximum irritability was reached when the K concentration was slightly below 5 m Eq. In the patients with heat cramps, any increase in K concentration that produced a decreased Na K ratio was greater than this optimum concentration of 5 m Eq. In Youngstown five patients with a decreased serum sodium concentration were given sodium bicarbonate intravenously in amounts varying between 3 5 and 7 0 grams. An injection of this quantity is sufficient to restore temporarily the normal Na K ratio in the serum. In three of the five patients the cramps were aggravated. In the remaining two there was no relief after this medication had been given. It may be concluded that, although the concentration of K is increased in patients with cramps, this increase in concentration and the altered Na K ratio are not intimately related to the pathogenesis of the disease.

7. The *calcium* concentration in the serum was increased in many of the patients on admission and in no patient was it observed to be decreased. A maximum concentration of 7 1 m Eq per liter or 14 3 mg per 100 cc was observed in two patients. A part of the increase in calcium concentration may be attributed to the calcium binding power of the increased protein concentration. This increased concentration of calcium was greater than the increase anticipated from the serum protein increase calculated by means of Peter's formula (64). His formula was derived from data of calcium and protein concentration that extended over a wide normal range, but did not include pathologically high protein concentrations. Unpublished data (65) obtained from a study of three patients with multiple myeloma, who had serum protein concentrations over 10 grams per cent, are worth noting. In each myeloma serum the calcium increase was not large and the calculated increase from Peter's formula was in close agreement. In these latter sera the globulin fraction accounted for the rise in total protein as in heat cramps.

In contrast to the protein and calcium concentrations in the serum from patients with myeloma that coincide with the protein and calcium ratio for normals are the data from the heat cramp patients. There is an increased concentration of calcium out of proportion to the increase in protein. This increase appears to be a function of

neither increased serum globulin nor decreased serum phosphate The only observations known of a high calcium and a high protein comparable to those found by us are from patients with Addison's disease (31) A similarity in the chemical data in these two diseases has been noted above Ionized calcium determinations were not done, but the concentrations were calculated according to McLean (66). None of the sera in which an unusual protein concentration was observed showed a calculated ionized calcium concentration beyond the normal range given by him

8 Serum *magnesium* concentration was determined on several of the blood samples In no patient was it observed to be decreased and usually it was 3 5 m Eq or more

e A change in *blood sugar* concentration in patients with cramps has been assumed without adequate evidence for some years In many of the steel mills dextrose has been employed for the prevention and treatment of cramps on the asumption that there was a deficiency of this substance in the body This assumption has not been verified by observation, in fact quite the reverse has been noted In animals exposed in high temperatures (60) and in men exposed to conditions favorable to the production of heat cramps (67), an increased concentration of blood sugar has been found In our Boulder City and Youngstown series, the average concentration of sugar on admission was between 100 mgm and 130 mgm per 100 cc The lowest observation was 91 mgm It is not denied that the workmen in the mills are doing hard work, but all of the available data indicate that their large caloric requirement is adequately met in their daily diet

In subjecting to a test the hypothesis of a "glycogen-deficiency" as a cause for cramps, the blood sugar concentration was increased in several patients who had cramps Four patients were given 50 to 100 cc of a 50 per cent dextrose solution, *i v* , and a fifth patient was given 250 cc of 10 per cent dextrose solution, *i v* The cramps were not relieved in any of these patients and three of them had an exacerbation of symptoms A sixth patient was given 1 0 cc of adrenalin chloride 1/1000 *i m* which increased the blood sugar concentration from 107 to 180 mgm per 100 cc No relief from cramps was observed over a four-hour period

f The *non-protein nitrogen* content of the serum was usually ele-

vated 10 to 25 mgm per 100 cc   The highest observation on any of
our patients was 106 mgm   Marsh (68) reported a blood urea nitro-
gen of 120 mgm on a patient with cramps   The elevation of the non-
protein nitrogen of the serum is not specific for heat cramps and is
frequently observed in patients suffering from heat stroke (67)   In
our Youngstown series there was an increase of the non-protein nitro-
gen of the serum in 75 per cent of the patients with cramps while only
37 per cent of those with heat stroke showed an increase   This may
be of minor diagnostic significance

   g The *white blood cells* are increased in number with a relative
increase in polymorphonuclear cells   The average increase that was
observed was from 4,000 to 6,000   The highest white count on ad-
mission was 18,200   The increase in the white count is a relatively
constant finding in heat cramps, and like the non-protein nitrogen, is
probably non-specific   That is to say, the increase may result from
the muscular activity in work as Edwards (69) has shown in man, or
from induced cramps as Formanek (70) has shown in dogs with strych-
nine poisoning   The effect of heat alone may also cause an increase
in the white cells in men (54) and in mice (71)

   The changes in concentration of many of the constituents of the
blood and serum are large and are observed only in diseases asso-
ciated with a profound disturbance of the acid-base equilibrium of the
body   The increases in serum protein concentration and cell volume
are of the order of magnitude observed in dehydration accompanying
severe cholera   The serum sodium, potassium, and phosphate may be
altered to the same extent as in a crisis from adrenal insufficiency
The calcium concentration is greater than is usually observed in
multiple myeloma and exceeded only by patients with a hyper-
function of the parathyroid glands   The white count and non-
protein nitrogen may be increased slightly   The concentration of
blood sugar is usually normal

XI THE URINE

   a The *amount* of urine (table IV) voided the first twelve hours after
admission is surprisingly large   The abundant sweating by the work-
men apparently does not lead to oliguria in most instances   Only
two of the patients in the Youngstown series were unable to void

TABLE IV

Balance studies of three patients with heat cramps

PATIENT	DATE (1934)	WEIGHT	URINE — Volume	pH	Titratable acid	Ammonia	Potassium	Sodium	Magnesium	Calcium	Total inorganic base	Chloride	Phosphate	Phosphate	Total nitrogen	Creatinine	Creatine	Chloride	Albumin	INTAKE — Fluid	Sodium	Chloride	Calories	REMARKS
		kgm	cc		m eq	m eq	m eq	m eq	m eq	m eq	m eq	m eq	grams	m eq	grams	grams	grams	m eq per liter		cc	m eq	m eq		
M S	June 27	58 4																100 6	Trace	1835	155 0	149 4	800	Admission
	June 27–28	59 1	415	5 5	22 4	37 9	11 2	33 0	5 8	8 7	58 0	31 5	0 59	20 2	6 0	1 20	0 23		Trace	1590	318 8	308 0	3030	
	June 28–29	60 1	690	6 2	21 4	50 6	12 1	94 2	7 6	12 7	125 7	110 3	0 70	26 3	3 9	1 30	0 21		Neg					
J D	June 1	65 2																10 2	Trace	1700	126 5	126 5	0	Admission
	June 1–2	66 5	335	5 5	13 4	24 5	28 8	10 2	3 9	2 2	45 6	2 6	0 34	8 0	3 0	1 20	0 21		Trace	2910	57 1	60 0	3000	
	June 2–3	66 8	1000	5 6	46 5		15 7	7 3		6 8	43 2	14 0	1 80	61	1 18	2 50	0 70		Neg	5890	346 4	337 7	2800	
	June 3–4	68 9	2000	5 8	31 0		12 1	24 5		6 5	47 3	6 1	1 10	38	7 2	2 20	0 31		Neg					
D N	July 13	51 8																20 0	Faint trace	1440	18 4	17 8	1210	Admission
	July 13–14	51 2	1010	7 4	5 6	10 6	18 8	43 1	6 7	7 7	87 2	8 0	0 10	5 9	5 8	0 90	0 36		Faint trace	5330	315 8	315 4	2760	
	July 14–15	53 2	1860	6 5	5 4	27 5	14 1	57 1	5 3	4 7	83 9	12 3	0 61	25 1	7 4	1 30	0 42		Very faint trace	5400	305 6	305 5	2680	
	July 15–16	53 4	3120	6 8	4 4	26 9	24 0	196 5	7 1	8 2	234 1	19 8	0 66	30 9	7 5	1 20	0 24		Neg	5000	315 6	315 4	2870	
	July 16–17	54 4	4300	6 7	4 3	49 1	15 2	309 0	9 1	12 1	346 5	32 8	0 75	33 5	8 9	1 30	0 35		Neg					

within the hour after admission   The average output in the hospital
the day of admission varied between 400 and 800 cc   The maximum
output observed in any patient the first day of observation was 3,600
cc   This subject had mild cramps and fluids up to 4,000 cc were
forced   The forcing of fluid in this patient was a therapeutic experi-
ment and the diuresis in the presence of dehydration was an interest-
ing finding   This result is similar to the observation of Heller and
Smirk (72) that in rabbits the kidneys will excrete urine following
fluid ingestion even though tissue dehydration is present   No evi-
dence was found to support Haldane's hypothesis (73) that there is a
shunting of blood away from the kidneys and cessation of excretion
of urine while working in a hot environment   Stated in a positive
manner this means that anuria is not to be expected in a patient with
heat cramps

b The *acid base equilibrium* in the urine

1 The *pH* of the urine was usually about 5 0 on admission and
increased to 5 8 or 6 0 on discharge   This degree of acidosis was
greater than was anticipated from the excretion of titratable acid
The daily excretion of titratable acid was usually more than 20 m Eq
during the period of hospitalization, but did not approach the amounts
noted in diabetic acidosis which is associated with a urinary pH
more alkaline than observed by us in heat cramps   A minor differen-
tial point was noted between the excretion of titratable acid by
patients with heat stroke and those with heat cramps   The amount of
titratable acid excreted in the urine of patients with heat stroke is
usually less than the amount excreted by patients with heat cramps

2, 3 and 4 The studies of the excretion of *ammonia, magnesium*
and *calcium* showed little that was unusual   These observations are
included principally for completeness in the acid-base balance of the
urine

5 and 6 The excretion of *sodium* and *chloride* in the urine will be
discussed together because of their intimate relationship to the patho-
genesis of heat cramps   Their respective concentrations in the urine
on the day of admission agreed in most patients within 10 m Eq
Edsall (10) was the first investigator to find an absence of chloride in
the urine from patients with heat cramps   At Boulder City and
Youngstown this observation was amply confirmed   In 24 of the 32

patients seen at Youngstown, the concentration of the chloride in the first admission specimen was below 40 m Eq per liter   Six of the remaining eight who had a concentration greater than 40 m Eq per liter on admission, subsequently showed a concentration below 40 m Eq   The finding of a chloride concentration above this amount in the initial specimen, even though the patient is suffering from chloride deficiency, may be readily explained   A concentrated urine containing an abundance of chloride may be excreted by the kidneys before the onset of cramps and not be voided from the bladder until after the attack, but this explanation is valid only for cramps with a sudden onset   The relative absence of sodium and chloride from the urine in severe cases may persist for several days   During this time the body is retaining sodium, chloride and water and gaining weight   The maximum chloride retention observed by us in Youngstown was 680 m Eq of Cl (40 grams if calculated as NaCl) in a three day period   At Boulder City the maximum retention of Cl over the same period was 735 m Eq   The average gain in weight during hospitalization by the patients in Youngstown was 4 4 pounds   Three patients showed no gain in weight and the maximum gain was 8 5 pounds

The minimum concentration of sodium and of chloride in the serum at which the excretion of these substances in the urine occurs may be deduced from our data   Assuming a minimal normal concentration in the serum of 100 m Eq per liter for Cl and 138 m Eq per liter for Na, the excretion of Cl and Na in the urine below these concentrations is not constant   When the serum chloride concentration was below 100 m Eq excretion of this electrolyte was extremely scant   Excretion of sodium occurred, however, in moderate amounts when the serum sodium was considerably below 138 m.Eq per liter   This dissipation of sodium with a lowering of the concentration of total base in the serum partially accounts for the diminished CO_2 combining power in some of the patients

7   The excretion of *potassium* in the urine on the admission day was decreased quantitatively, similarly to the decrease in sodium   No attempt is made by the body to maintain the total base excretion by an outpouring of potassium   This is consistent with the indirect observations by Dill (47) that sweating is accompanied by an extra-renal loss of potassium as well as of sodium and of chloride in the sweat

8   An increased excretion of *phosphate* in the urine was noted by Edsall (10) to occur concurrently with the diminished chloride excretion   This increased excretion is not a constant finding in heat cramps (14)   It was occasionally observed in the patients in Youngstown when the serum phosphate concentration was elevated   The increased breakdown of phospho creatine in the muscle during or after the paroxysms of cramps is suggested without evidence as the cause of this phenomenon

   c   The *creatine* excretion in the urine also suggests increased phospho-creatine breakdown in patients with heat cramps   Edsall (10) observed a daily excretion as great as 4 2 grams of creatine from a patient with very severe heat cramps   He believed that this was caused by degenerative processes that were associated with the pathogenesis of the spasm   It is now known that many patients with heat cramps do not show this excessive excretion of creatine (14)   The majority of the severe cases in Youngstown, however, did show it   Three of these patients excreted more than one gram of creatine on the second day of their illness   In each instance there was a return to minimal amounts on the third day

   d   The *total nitrogen* excreted in the urine was increased on the second and third day of hospitalization, in more than 50 per cent of the patients   The maximum daily excretion of nitrogen observed was 22 grams   There was an approximate correlation between nitrogen excretion and severity of cramps, the patients with severe cramps usually excreted the largest amounts of nitrogen in the urine

   e   *Albumin* was frequently found in the urine on the first and second days following an attack of cramps   Hyaline casts were observed in the urine sediment from many of the patients   The casts were not observed after the first day   In all patients the urine was free from albumin on discharge   The evidence that the albumin may be a function of the high temperature and not singularly related to heat cramps is furnished by the studies on heat stroke   In this condition albumin is a common finding (54), (74)

   The changes in the urine from patients with cramps were sufficiently large to permit them to be employed as diagnostic aids   The pH on admission was about 5 0, but the excretion of titratable acid was not appreciably increased   In the admission specimen, there was a much

diminished or a negligible amount of chloride   The reappearance of chloride in the urine was delayed from one to three days   The excretion of Na was comparable with the excretion of Cl   Phosphaturia and creatinuria were frequently observed   The increased excretion of these substances in heat cramps may be caused by a disturbance of the otherwise normal metabolism of muscle   The excretion of total nitrogen was usually increased on the second day in the hospital Albumin and casts were constantly observed in the admission specimens, but not in the urine obtained at discharge

XII DIFFERENTIAL DIAGNOSIS

The diagnosis of cramps that persist after admission to the hospital is not difficult in a subject who has worked in a high environmental temperature   Cessation of cramps before admission without recurrence after admission often makes a diagnosis more difficult and permits a possible confusion with other similar conditions

Any discussion of the differential diagnosis should proceed from the premise that heat cramps are not a symptom, but a clinical entity. In most of the work previous to the contributions of Edsall, cramps were considered a symptom only of heat stroke (2), (6), (75)   Following Edsall's paper, heat cramps have been placed in their own category apart from heat stroke and heat exhaustion by Moss (12), Welsh (37), Stengel (76) and others   This differentiation has not been accepted by Morton (32), Fiske (33) and Smith (77), Marsh (78) among the recent writers, nor have the Germans considered this a separate entity, if we may judge from a recent review of the ill effects of heat by Franz (79)

a It was observed in 1932 (14) that *heat cramps, heat stroke* and *heat exhaustion* had a common point of origin   They are observed in men doing hard work in high temperatures and may be associated with profuse sweating (80), a large fluid intake and a diminished urine output   The comparison beyond this point reveals less similarity

An important point in the differential diagnosis of these conditions is the duration of the heat wave before the onset of symptoms Willcox (81) believed that one or two very hot days were not necessarily followed by a number of patients stricken with heat prostration It was the succession of several hot days which were considered to be

dangerous   Hutchinson (20) and Hamilton (82) confirmed this observation   Quite the reverse is true for heat cramps   The incidence of cramps is greatest the first few days of a heat wave (7), (11), (29)

The physical examination is of further aid in the differentiation The temperature in patients with heat stroke is frequently elevated to 108° and 110°F (23), (83)   In heat exhaustion it may be subnormal (11), (84)   In patients with heat cramps the temperature is generally normal   The pupils may be constricted in heat stroke (84), but are unchanged in cramps   Diarrhea is a frequent accompaniment of heat stroke (84), (85), but not heat cramps   The rapid recovery from cramps with proper treatment is a striking characteristic of this disease (14), (38)   Recovery is less rapid in severe cases of heat exhaustion and heat stroke

Knowledge of certain reactions of the nervous system to excessive heat is useful in arriving at a correct diagnosis   The only abnormal reactions observed in patients with cramps are slight changes in the deep reflexes (11), (29), mild headache and vertigo (6)   In contrast, heat stroke and heat exhaustion are frequently accompanied by delirium, convulsions and coma (83), (86), (87)   Hemiplegia and paraplegia are infrequent complications observed by Weisenburg (35) in sun stroke (heat stroke)

A mention of sun stroke should be made in this differential discussion   The above arguments considered under heat stroke are applicable to sun stroke   That is, they are applicable if sun stroke is accepted as synonymous with heat stroke   Such a view is held by Shattuck (88), Colcord (89) and the author

b and *c Nocturnal cramps* (4), (90), (91) and *cramps following violent exercise* (92) are not easily distinguishable from heat cramps Heat cramps may have a long latent period and not develop until several hours after work has ceased   Because of a time of onset similar to nocturnal cramps, any workman who develops muscle spasms during sleep after working in a high temperature should probably be treated as a patient with heat cramps   The etiology of cramps following exercise is being investigated at present by this laboratory   Preliminary evidence suggests a pathogenesis similar to that for heat cramps

d Abdominal colic should be considered when making a diagnosis of cramps confined to the abdomen or abdominal wall   When cramps are present in other parts of the body in addition to the abdomen, no confusion exists   The diagnosis of cramps confined to the abdomen alone is not an easy one to make and to confirm by laboratory data In Youngstown five patients were admitted with a diagnosis of heat cramps confined to the abdomen   During their stay in the hospital none of them had cramps elsewhere   None of the five had the typical chemical changes observed in the serum and urine from patients with heat cramps of the extremities   The final diagnosis of one patient with questionable heat cramps of the abdomen was gastric colic from a dietary indiscretion   Another patient had a strongly positive blood Wassermann reaction in addition to absent pupillary reflexes.   He was discharged with a diagnosis of gastric tabes   The symptoms in the other three were not adequately explained   The ingestion of large quantities of cool water may produce gastric colic (93)   It is possible that this syndrome is more prevalent than was appreciated by us

Less frequently encountered pathological states that might be confused with heat cramps are delirium tremens, strychnine poisoning (28), epilepsy, tetany, trichinosis, uremia (15), hysteria and writer's cramp   A satisfactory history and physical examination should substantiate a diagnosis of any of the above conditions, if they are present

The conditions that may be considered in a differential diagnosis of heat cramps are heat stroke, nocturnal cramps, gastric colic and convulsions   Heat stroke may be confused with cramps only when the cramps are mild and cease before admission to the hospital   Nocturnal cramps in men susceptible to heat cramps should be treated as heat cramps   Gastric colic was very bewildering in patients with mild symptoms and the study of them in the future may yield pertinent information   Convulsions as a symptom of organic disease may be excluded only after a complete study of the patient

XIII PATHOGENESIS

Theories of the pathogenesis of heat cramps have varied considerably since the disease was first recognized   In 1898, Stone (94) presumably considered the mechanism to be a depletion of salt and fluid from the body, since he proposed the use of hypodermic saline solution

in their treatment   In 1903 Edsall (8) proposed, as the pathogenic process, an acute degeneration of the muscles   Sometime later an infectious theory was considered, but quite inadequately supported In recent years interest has again reverted to pathologic physiology to explain the underlying mechanism that causes the disease   Haldane in his discussion of a paper by Moss (12) in 1923 stated that he believed that miner's cramps could be attributed to 'water poisoning' He explained the production of "water poisoning" (73) by an inability of the kidneys to excrete the excess of ingested fluids   No inability of the kidneys to excrete fluid was observed by us in most of the patients in Youngstown or in Boulder City   Further, if "water poisoning" exists because of an excess of water, the osmotic pressure of the serum should be decreased   Such a decrease was observed in only 3 of the 13 sera from patients with cramps on which osmotic pressure was determined   The sera obtained on admission from 4 of the patients showed an increased osmotic pressure and in the remaining 6 it was normal   These data suggest that the lowering of the concentration of certain electrolytes in the serum from loss in the sweat is associated with a concomitant increase in other constituents and that the osmotic pressure is maintained

a In the serum from patients with heat cramps the principal reduction of inorganic base is in the sodium fraction and of the acids, in the chloride fraction   *This lowering of the sodium and chloride in the serum, from loss in the sweat without adequate replacement, is considered to be the principal causative mechanism in the production of heat cramps*   Direct evidence is not available to show that the diminution in the concentration of electrolytes in the blood is followed by a similar diminution of these substances in the intercellular spaces But it is generally assumed that the concentration of electrolytes in the serum and in the tissue spaces is approximately equal   If these are the facts, then a loss of water and salt from the blood is followed by a partial replacement from the tissues   In the condition under discussion there is a loss of salt and water from the body with a replacement principally of water   If this major process is continued irrespective of the secondary processes, there will be a lowering of the sodium and chloride concentration below normal   When the critical level for sodium and chloride is reached in the working subject,

muscle cramps will occur   It seems likely that this critical level is a function of individual susceptibility, acclimatization, the length of the prodromal period and intensity of work.

  b A *disturbance of carbohydrate metabolism* has been assumed at various times to be intimately related to the pathogenesis of heat cramps   The studies by Sutton in 1909 (95) probably furnished the evidence on which this assumption is based   He concluded from a study of the respiratory quotient from men exposed to a wet bulb temperature of 88°F that there was a five-fold increase in carbohydrate consumption   An increased consumption of carbohydrate in men exposed to high temperature might be a result of an increased demand for sugar or a disturbance of the otherwise normal metabolic processes of carbohydrate breakdown and resynthesis (96)   There is no experimental evidence to support either hypothesis   Blood sugar determinations on the Boulder City and Youngstown patients showed nothing to suggest a hypoglycemia   Lactic acid determinations likewise showed slight variation from the normal   Finally, elevation of the blood sugar either by injection of adrenalin or increased intake of dextrose aggravated the moderate and severe cases of cramps   It may be concluded that there is little evidence to suggest a disturbance of carbohydrate metabolism as a factor in the etiology of heat cramps

  c The *artificial production of cramps* in animals and in men from overheating alone has not been observed   In 1925 Flinn (58) studied the exposure of dogs to high temperatures and was not able to produce cramps or tetany   With the present knowledge of the etiology of cramps, it is clear why he was not successful   Dissipation of heat in dogs is accomplished not by sweating as in man, but by evaporation of moisture in the lungs and respiratory passages with only a minimal loss of body salt   This loss of salt by the dogs is not of sufficient magnitude to produce a lowered concentration of serum chloride (97)   Weir and Rountree (98) were successful in lowering the concentration of plasma chloride in dogs by the use of hypertonic dextrose infusions, but observed muscle twitchings only.   These muscle twitchings might conceivably have been the prodromal signs of cramps

  The production of a cramp-like syndrome in man in a hot room has been observed by several workers   Adolph and Fulton (99) kept human subjects in a saturated atmosphere at 102°F for as long as the

latter were able to endure it   After the first few minutes they reported
a feeling of extreme discomfort   This discomfort was accompanied
by a tingling in the hands followed by tetany and cramps   Simpson
(100) made similar observations on patients that were treated with
high frequency currents   His observation that the drinking of 0 6
per cent NaCl solution relieved these unpleasant sensations is im-
portant   The presence of tetany in these experiments suggests that
the muscle disturbances they observed were not uncomplicated heat
cramps   McConnell and Sayers (101) were unable to produce cramps
following the ingestion of 900 cc of cold water after profuse sweating
in a hot room for one hour

XIV PATHOLOGICAL ANATOMY

There are very few necropsies reported on patients dying from heat
cramps and complete pathological descriptions of these are not given
Elliot (11) briefly described the gross examination of a twenty-six
year old negro who had died six hours after the onset of cramps
This patient did not lose consciousness until shortly before death
The pertinent observations mentioned by Elliot were the rigid con-
traction of the left ventricle, congestion of the lungs and congestion
of the gastric mucosa   Contraction of the left ventricle and con-
gestion of the lungs have been observed (77) at autopsy in patients
who have died presumably from heat stroke and not heat cramps
Whether these findings are directly related to the effects of high tem-
peratures or are only incidental, will be decided only after further
investigation

XV TREATMENT

A large number of therapeutic measures have been employed in the
treatment of heat cramps   Most of these measures have been based
on impressions handed down in domestic and professional circles
They are empiric in nature and symptomatic rather than specific in
providing relief

   a   Rest is one therapeutic agent that is easy to provide and is bene-
ficial to the afflicted   It is obligatory for all severe cases and generally
available for the milder ones   Recovery from cramps with no other
therapy than rest has long been recognized by workmen, but not

thoroughly appreciated by physicians   The failure to appreciate the frequency of spontaneous recovery has given rise to exaggerated confidence in the efficacy of certain drugs   The evaluation of the utility of any therapeutic procedure in the treatment of cramps is valid only when it is recognized that a spontaneous recovery is possible In the Youngstown series, 12 patients received no therapy the day of admission other than food and rest in bed   All of these patients had mild cramps, but their recovery was rapid and satisfactory   The explanation of this recovery is a simple one   The loss of body fluid and electrolytes in the sweat which produced a disturbance of the normal equilibrium had not progressed to a serious degree in the mild cases   Cessation of work and diminution of the rate of sweat loss occurred early enough to allow a partial readjustment of the disturbed equilibrium with alleviation of symptoms

   b *Whiskey, brandy, vinegar* and *turpentine* are domestic remedies that have their proponents   The chief benefit from any of these agents is probably derived from their action as cardiac stimulants or counter-irritants   There is no evidence that any of them exert a specific therapeutic effect

   c *Morphine* is one drug that is frequently used in the treatment of severe cramps, but few observers have been satisfied with its amelioration of pain (7), (10), (28), (37), (55)   In our series morphine in $\frac{1}{4}$- to $\frac{1}{2}$-grain doses was given hypodermically to three patients   In no instance did this stop the cramps and in no instance did this relieve the pain   Welsh (37) gave as much as $\frac{3}{4}$-grain within two hours to one patient with cramps without any subsidence in symptoms   His experience with *apomorphine* is quite the reverse   He found that given in a dose of $\frac{1}{20}$- to $\frac{1}{12}$-grain immediate relaxation was produced The emetic action was prompt and was usually followed by extreme prostration   We have had no experience with this drug in cramps as it is believed that vomiting and prostration are to be rigidly avoided *Bulbocapnine* has been suggested by Cobb (102) because of its influence on striated muscle   There is no report of any one having used it in the treatment of heat cramps

   d. *Hot packs* have been in vogue at various times   They afford a certain degree of temporary relief if water is not ingested simultaneously   The probable action is to increase perspiration   The sedative

effect on the somatic musculature may also be beneficial   The sweat that is produced by the hot pack contains a lower concentration of Na and of Cl than the serum and the ultimate effect is to raise the concentration of these electrolytes in the remaining body fluid   This temporary increase in concentration may be sufficient to relieve the patient of cramps   The duration of relief afforded is very short, however, and if the sweating is followed by an increased consumption of water, the cramps are apt to return   Three patients were treated with hot packs and allowed water by mouth in the Youngstown series, and in each patient cramps continued from one and a half to six hours

c Castor oil and *saline laxatives* were used by Meyers (7), but no comment is made of their efficacy   The vegetable purgatives do little more than promote general well being, if the patient is constipated   Saline purgatives may exert an additional action   If an increased concentration of potassium in the body fluid accompanies the cramps, the loss of intestinal fluid may lower slightly this concentration

f Calcium chloride in 4 to 6 gram doses was used by Cazamian (24) intravenously and by mouth in the treatment of heat cramps   His justification for using this medication was a theoretical one   His explanation of the cause of cramps was a lowering of the concentration of calcium in the serum following increased excretion of calcium in the sweat   Our data do not substantiate this hypothesis as the serum calcium concentration was observed to be increased in most of the patients with cramps   The possible sedative action of intravenous calcium salts was investigated in 3 patients in Youngstown without therapeutic benefit   Calcium gluconate and calcium chloride were given in doses varying between 2 and 5 grams

g Amyl nitrite was used by Coplin (6) with success in the treatment of cramps complicated by headache   In the early days of treatment, *chloroform* anaesthesia was frequently necessary (28), (37)   Such drastic therapy is of historical interest only

h Locke's solution was given to one of our patients   No previous record of its use was found in the literature   In this patient cramps persisted for several hours after its administration

i. Sodium bicarbonate is recommended by Morton (32) for heat cramps and heat exhaustion   To 4 of our patients, sodium bicarbonate in 3 5 to 7 0 gram doses was administered *i v*   In each patient

cramps could be induced afterwards   It seems likely that the beneficial effect attributed by Morton to the sodium bicarbonate should have been given to the salt which was used in conjunction with it

j Dextrose ingested by mouth or injected into the vein is a popular form of therapy at present   In spite of its extensive employment, there is no published series of cases justifying its therapeutic use   Its employment has been empirical and the therapeutic results have not been critically examined   Mild cases are apt to recover without medication and when dextrose has been given to these patients, the credit for recovery has been misplaced   Another explanation of the apparent benefit from dextrose is the common practice of using a saline solution as the vehicle for this substance when it is given intravenously   Relief from such a mixture has been attributed falsely to the dextrose   The treatment of heat cramps by the administration of dextrose has been investigated by us in 5 patients   In all of these the persistence of cramps after the giving of dextrose necessitated the subsequent administration of normal saline solution   After the saline infusions no cramps could be induced   It was our experience that dextrose was not effective in the treatment of heat cramps

k Saline solution is the last therapeutic agent that will be considered   The use of saline solution is not new in the history of the treatment of heat cramps   The earliest report of its use was in 1898 by Stone (94)   Ten years later Elliot (11) gave saline enemata to patients suffering from heat stroke or heat cramps   No discussion of the beneficial effects of saline are given in either instance nor was either observer enthusiastic about its use   In 1918, Pryor (36) advised either dextrose or saline for the treatment of heat cramps occurring in the men on the ships of the United States Navy   Haldane's (45) reemphasis of the importance of salt in treatment was not widely followed and as recently as 1934 at least one large steel company advised against its use in most patients

The choice of the route for the administration of the saline solution is optional   None of our patients were in shock, nevertheless, the intravenous route was invariably used   Willcox (81) preferred to inject the solution under the skin   Our principal objection to this route is the pain suffered by the patient during the treatment   In the patients in our series who received normal saline solution, 600 cc

to 1,000 cc were given intravenously the first six hours and repeated if the patient were markedly dehydrated   After the first few hours the patients were generally able to begin taking salt by mouth   At Boulder City a high milk diet was used to achieve this purpose   At Youngstown one-gram salt tablets were given every hour by mouth through the day until fifteen tablets had been taken   In no instance were there any gastro-intestinal symptoms observed that were attributed to the salt ingested

In our hands the use of normal saline solution in all severe cases was highly satisfactory   Every patient that was given saline solution alone was relieved of his cramps before the end of the initial infusion   All attempts to induce cramps after the infusions were unsuccessful   In view of the etiology of heat cramps and the success of saline therapy at Boulder City and Youngstown, it is believed that this may be considered a specific therapeutic agent

XVI PREVENTION

a A state of *good health* among the workmen (103) has long been stressed and is extremely important in the prevention of heat cramps   Most of the mill men in Youngstown on inquiry regarding their individual method of prevention gave first consideration to this factor   The enforced absence from work of all men not in good health would decrease the incidence of heat cramps   Frequent physical examinations are a necessary part of any adequate plan of prevention

b *Suitable environment* when off duty and at home has been emphasized by most observers   The need of good food and restful sleep is especially important in the summer   Failure to obtain these partially explains the high summer incidence of cramps

c The *diet* of men exposed to conditions favorable for the development of cramps may need modification in some instances but usually is adequate and satisfactory   The belief that the limitation of protein is desirable for men working in a hot environment is widespread (103), (104)   There is little evidence to support this   The need of an adequate protein intake is obvious for men doing hard physical labour   A large proportion of carbohydrate foods may supply the remaining necessary calories   Of equal importance in prevention of cramps is an adequate mineral intake   An average NaCl intake of 15

grams daily is probably necessary for men doing hard work in the summer (47), (105)

A liberal fluid intake is imperative for workmen losing several liters of fluid in the sweat each day   Van Zwalenburg (106) believes that a liberal intake may be useful in the prevention of cramps   This is undoubtedly a fact, if an adequate amount of salt is ingested simultaneously

d *Oatmeal water*, according to Thrower (107), is only one way of gaining fluid and is not specific   The mechanism of its action has not been explained (108)   It is possible that if taken in sufficient quantities certain of the mineral requirements may be supplied with the fluid

e *Whiskey* and *beer* have been attributed preventive properties (32), (36)   It is commonly accepted that the coal miners in England who drink beer do not suffer from cramps   An important observation regarding these miners is their addition of salt to their beer before consumption   The probable effect of whiskey in small doses is supportive

f *Powdered sulphur*, the "puddlers' remedy," is one of the older medicines used as a preventive   The sulphur may be ingested, dusted in the shoes, or worn about the legs enclosed in a small pouch   In the latter use it resembles asafoetida   The origin of the use of sulphur is probably associated with the drinking of water from hydrogen sulphide springs   One sulphur spring in Youngstown enjoyed a fine reputation for the prevention of cramps   Analysis of the spring water showed it to be rich in sodium chloride as well as in sulphur   The taste was principally a sulphur one, while the preventive action was probably a function of the sodium chloride concentration

g In prevention as in treatment *dextrose* occupies an important place   Dextrose in two-gram packages is dispensed by several of the steel mills in this country   Frequent ingestion of this amount on hot days is advised   Such a measure has not been attended with the success which was expected   The explanation of the prevention of cramps by the ingestion of dextrose is similar to the explanation of its curative power   Both presuppose a deficiency of glycogen or impaired mobilization   Glover (29) speculated on the possible aid in mobilization and utilization of NaCl from the ingestion of dextrose

There is no evidence to support such an hypothesis   In summary, dextrose has been and still is widely used for the prevention of cramps It has many supporters, none of whom has furnished experimental or statistical evidence of its merit   Any benefit derived from dextrose is probably symptomatic and not specific   Dextrose is a readily assimilated food, a source of quick energy, useful in the prevention of fatigue, but not specific in the prevention of cramps

h The ingestion of *sodium chloride* for the prevention of heat cramps is sound theoretically and has been beneficial when practised   Since the cause of cramps is essentially a loss of salt in the sweat and urine, that is greater than the intake, the added ingestion of NaCl will prevent this negative balance   The salt may be given in dilute concentration in the drinking water (109), dispensed in compressed tablets (29), or taken with the meals (14)   These are mentioned in order of their efficiency   The addition of salt to the food is neither regular nor reliable   The craving for salty foods is not a dependable criterion of a low salt reserve in the body   Many men are prejudiced against the liberal use of salt at the table or have no taste for it   Occasionally meals are skipped and thus no salt at all is ingested   The dispensing of salt in compressed tablets at the drinking fountains has been tried extensively in the Cleveland district with highly satisfactory results Engel (105) reports 171 patients suffering from heat in one steel mill between 1920 and 1928   Since 1926 there has been a progressive introduction of salt dispensing machines in the various departments In the three years after 1928 not a man reported off duty because of cramps   Glover (29) has almost as convincing evidence from a plant where cramps had been very common before the introduction of salt prophylaxis   The experience of the mills in Youngstown is less favorable   The ingestion of the tablets is purely optional with the men Many of the men who need additional salt are prejudiced against its use in this form   Salt tablets of one gram each are not palatable, especially for a man doing hard work   Seven of the thirty-one patients studied at Youngstown had taken salt on the day of admission to the hospital   In five patients the number taken was small and probably insufficient   In another, the number was large and the patient had had nausea and had vomited many of the previously ingested tablets

The general administration of salt in amounts sufficient to protect

against cramps can best be achieved by its addition to the drinking water   Moss (12) advised the use of NaCl and KCl in the proportion of 60 to 40 per cent in the drinking water   Oswald (110) recommended a saline drink of 0 14 per cent KCl and 0 21 per cent NaCl Drinking water containing NaCl in 0 25 to 1 0 per cent concentration has been used successfully in the prevention of heat cramps on the ships of the United States Navy (111), (112)   Bock (21) tried out several concentrations of sodium chloride from 0 1 to 0 5 per cent on unaffected workmen in Youngstown   He concluded that the 0 1 to 0 15 per cent was the preferable concentration   Such a solution can be taken cool without a perceptible saline taste   This solution allays rather than promotes the sensation of thirst   Stronger solutions increase the sensation of thirst and may also cause water retention (112)   The highest serum chloride concentration observed by Bock after the ingestion of a 0 5 per cent solution during a day's work was 112 m Eq   Such high serum chloride concentrations are neither desirable nor necessary   The concentration of chloride in the serum from the same men several days later, after taking 0 1 per cent saline solution, were all within the normal range

The hazards to be considered from general salting of the drinking water are not significant   A workman with kidney disease, heart disease, or any condition in which edema may be a symptom, is infrequently found in the industries where cramps are common   It seems unlikely that any harmful effects are to be anticipated where the men are physically able to perform hard work and to sweat profusely

It is our conclusion based upon experimental evidence that sodium chloride is useful in the prevention of heat cramps   It is our belief that the ideal method of supplying the salt is to provide it in the drinking water in a 0 1 per cent concentration   Men on jobs in high temperatures should be allowed only this water or similar salted drinks while at work

XVII PROTOCOLS

Case 1

Mr M S , a married white man of 42, entered the hospital on June 27, 1934, complaining of cramps in his fingers, toes, and right side of the body, and a slight frontal headache   On admission 45 cc of blood was drawn from the brachial artery

Past History   Born in Austria, he had been a steel mill worker since the age of fourteen   He worked in the German steel mills up to twelve years ago, and in the U S mills since that time   He had never had any cramps until the winter of 1933   At that time generalized cramps forced him to stop work   In 1911 he had pneumonia followed by a satisfactory recovery   In the World War on the Eastern front he had a toe shot off   The past ten years he had lost about 25 pounds   There was no recent weight loss

Present Illness   He had not been working the ten days before admission because of lack of orders at the mill   The day before admission was a hot day, but he had no complaints except for a very mild headache which was not unusual   He slept nine hours that night   He ate a good breakfast and had a bowel movement the next morning   The afternoon of admission he had a mild recurrence of the headache   A large amount of water was consumed and he believed that he perspired more profusely than any day he could remember   In the afternoon he was compelled to do the work usually done by two men   He finished the shift at 4 P M feeling very tired and then took a shower   Shortly after, painful cramps developed in his hands, fingers, and toes   The cramps came in paroxysms that persisted from 3 to 5 minutes   He reported for medical attention, was brought immediately to the hospital, and was admitted about 40 minutes after the onset of cramps

Physical Examination   Temperature 99 6°F p r , pulse 106, respiratory rate 22, blood pressure 160/98   The skin was warm and the perspiration moderate   The head, chest, and abdomen showed nothing abnormal on examination   There was some clubbing of the fingers and toes   The biceps and patellar reflexes were exaggerated   No fibrillary twitchings of the skeletal muscles were seen   The attempt to induce cramps in the hands was not successful on admission   One hour later the cramps returned spontaneously and continued intermittently through the night

Diagnosis   Mild heat cramps

Course   The patient was given no specific therapy the first day in the hospital and cramps recurred spontaneously   The second day a high salt diet was started, and he had no return of cramps   He stayed in the hospital 48 hours and gained 1 7 kgm and retained 290 m Eq of chloride in this period

Case 2

Mr J D , a divorced, colored man of 38, entered the hospital on July 1, 1934, complaining of generalized cramps in his extremities and in his abdominal wall   On admission 45 cc of blood was taken from the brachial artery

Past History   Born in Virginia, he had worked steadily in the sheet mills for 14 years, up to 1929   In 1918 and 1928 he was treated for gonorrhea   He consumed moderate amounts of hard liquor but did not classify himself as a steady drinker   He had never been exhausted by the heat Seven years ago he had generalized cramps in his arms and legs   They were not severe enough to cause him to seek medical attention and they subsided with treatment at home

Present Illness   The day of admission was the first sheet mill work the patient had had for four years.   During that period he had only odd jobs of short duration   Two days before admission he consumed large amounts of alcohol, but had eaten his meals regularly   He slept well the night before admission   He ate a good breakfast and had a bowel movement before going to work   The day was hot, he worked very hard, perspired profusely, and had not appetite for lunch   At 3 P M he felt weak, became slightly dizzy, had a little nausea but did not vomit   Shortly after, he was transferred to an easier job   He began to have cramps in his arms and legs but was able to finish the shift   He had a shower bath, felt better, and went home   On his arrival home, he was seized with severe cramps in his extremities, his neck, and along his back   The muscles knotted up in hard bunches and became excruciatingly painful   The muscles in the abdominal wall became involved shortly afterward, and this was followed by vomiting It became impossible for him to walk and he was brought to the hospital by ambulance at 7 P M

Physical Examination   Temperature 99 4°F pr , pulse 108, respiratory rate 20, blood pressure 100/72   His skin was warm and he perspired moderately   Nothing was discovered on examination that was unusual except the cramps   The patient appeared to be in extreme pain from cramps in his arms, legs, abdominal wall, and back   The cramps were intermittent in character and 2 to 3 minutes in duration   The cramps were accompanied by paroxysms of extreme pain   On palpation the affected muscles felt stony hard   The cramped muscles were not tender to palpation nor could the cramps be massaged away   When the hands and arms were involved, the affected member would be flexed with such force that it was impossible for the examiner to extend it, without some fear of breaking a bone   The deep reflexes were present

Diagnosis   Severe heat cramps

Course   The cramps did not subside with rest in bed, and 50 minutes after admission he was given 50 cc of 50 per cent dextrose intravenously The next 25 minutes, the cramps returned with greater severity than before It was necessary for the patient to walk the floor to obtain slight relief

At 8 15 P M he was given morphine sulphate gr 1/4 by hypodermoclysis There was little relief from the medication after 35 minutes   Two hundred and fifty cc of 10 per cent dextrose was then administered intravenously Shortly after the injection of this solution there was a period of freedom from cramps only to have them return in greater severity than before The patient felt that he could no longer tolerate the pain and morphine sulphate gr 1/4 was repeated, followed at 10 30 P M by 800 cc of normal saline solution intravenously   When about 200 cc of the saline solution had been given, the patient relaxed, said that he had no more cramps and was extremely tired   He slept for $1\frac{1}{2}$ hours after this   At midnight he had a very mild cramp in a finger and then slept until morning   There was no subsequent return of his cramps   He stayed in the hospital two days During this time he gained 3 7 kgm in weight and retained 438 m Eq of chloride

August 3, 1934   He was interviewed and had been working two or three days each week since discharge   Two weeks before, after a period of unemployment he had mild cramps in his arms

Case 3

Mr D N , a divorced, white man of 47, entered the hospital on July 13, 1934, complaining of cramps in his extremities, back, and abdomen   On admission 45 cc of blood was drawn from the brachial artery

Past History   Born in Pennsylvania, he had worked in the steel mills since the age of 16   He denied having had any heat cramps until 1932 The past two summers he had had mild cramps but was not forced to stop work on their account   He had been a heavy consumer of alcohol for many years   Ten years ago he had a chancre that was treated by cautery He was given no other anti-luetic therapy   His appendix was removed at the age of 17   The past five years he has been slightly short of breath on exertion, but had no other symptoms of organic disease

Present Illness   Six days before admission the patient began a two-day drinking bout because he was not working   He ate very little on those days   Four days before admission he worked for two days and had no difficulty doing the work, but the days were hot and he had mild cramps in his hands   They were not severe enough, however, to prevent his working his full shift   The next two days he did not work, drank again, ate very little, but denied having been intoxicated   The day of admission he felt well, ate a good breakfast, and went to work   After one half hour of work mild cramps returned in his thighs and calves   He continued to work and con-sumed large quantities of water   After working about two hours he became

weak   This was followed by severe generalized cramps which forced him
to stop work   He was sent to the hospital but was able to walk to the ward

Physical Examination   Temperature 99 4°F p r , pulse 90, respiratory
rate 20, blood pressure 162/106   The skin did not feel hot nor was the
perspiration abundant   The head, neck, and chest were not remarkable
on physical examination   The abdomen was tense during an attack of
cramps but not stony hard   The liver was palpated four cm below the
costal margin in the nipple line   There were small varices of the veins of
the legs   The biceps reflexes were bilaterally absent   The other deep
reflexes were present   Diffuse fibrillary twitchings of the muscles of the
arms and legs were observed followed by cramps of the same muscles   The
cramps came in paroxysms lasting 30 to 60 seconds at 5 to 15 minute
intervals

Diagnosis   Moderate heat cramps

Course Shortly after admission the patient was given 2 cc of 25 per
cent MgSO₄ intravenously   During the next hour cramps were present in
undiminished intensity   The MgSO₄ was repeated and the cramps con-
tinued   Two and one-half hours after the second injection of MgSO₄, 10 cc
of calcium gluconate was given   Three hours later the calcium gluconate
was repeated   Mild cramps continued that day and could be induced
easily the next morning   Twenty-four hours after admission the cramps
had completely subsided, but the patient began to talk incoherently and
had visual hallucinations   He recovered from his cramps but was kept in
the hospital for one week because of his hallucinations   A subsequent
diagnosis of chronic alcoholism was made   The magnesium sulphate and
calcium gluconate were given to observe their therapeutic effect

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CAROTID SINUS SYNCOPE AND ITS BEARING ON THE MECHANISM OF THE UNCONSCIOUS STATE AND CONVULSIONS[1]

A STUDY OF 32 ADDITIONAL CASES

EUGENE B. FERRIS, JR, M D, RICHARD B. CAPPS, M D AND SOMA WEISS, M D

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston)

CONTENTS

INTRODUCTION

Dizziness and fainting, with or without convulsions, are common clinical manifestations, and yet relatively little effort has been made to determine the mechanisms involved in their production Owing to the transient and unexpected nature of such attacks, one seldom has an opportunity to observe and study them carefully Although loss of consciousness has been investigated to some extent in such conditions as epilepsy (1), certain cerebral diseases and head trauma, no definite etiology or pathology is evident in the great majority of cases and such a symptom is often looked upon as being "functional " It is in this latter group of "functional" cases that we are particularly interested in this study

It has been generally assumed that fainting is due to a cerebral ischemia caused either by a decreased cardiac output or by a temporary vasomotor collapse with consequent fall in blood pressure, or that it is due simply to "functional" causes Considerable data are available concerning cardiac syncope Temporary loss of consciousness has been shown to occur in angina pectoris (2) (3), coronary thrombosis (4), dissecting aneurysm (4) and also in the various paroxysmal arrhythmias (5) (6) (7) (8) (9) (10) (11) (12) (13) (14) Although most of these conditions are usually associated with organic heart disease, cardiac syncope can be entirely neurogenic in origin [2] Fainting in these instances of cardiac syncope is generally assumed to have been caused by cerebral ischemia as the result of a diminished cardiac output

Fainting of vasomotor origin has only been studied in some of its aspects Postural hypotension, which is an inability of the cardiovascular system to maintain the blood pressure when the body is in the erect position, may lead to dizziness and syncope (15) (16) (17) Likewise, in "pleural shock," syncope may be associated with a marked fall in blood pressure as a result of pleural stimulation (18)

[2] Weiss, S Syncope and Related Syndromes, Oxford Medicine, New York, Oxford University Press (In Press)

(19)   The most common type of fainting is that which occurs in apparently healthy persons as a result of such stimuli as the sight of blood, overheated crowded rooms or strong emotional reactions This has been termed "vaso-vagal" syncope by Lewis (20)   Such attacks are accompanied by pallor, sweating, fall in blood pressure, particularly the systolic, and often by bradycardia (21) (22) (23) (24) (25) (26) (27)   From the limited data available it would appear that the mechanism involved in the loss of consciousness is simply a fall in systemic blood pressure dependent on a systemic vasodilatation, with the bradycardia playing a variable rôle

That convulsions and temporary loss of consciousness can occur without significant changes in the blood pressure or the heart rate in patients free of epilepsy or cerebral disease has been definitely shown by Weiss and Baker in their work on the carotid sinus syndrome   A report including two such cases (nos 8 and 14) with a review of the literature on the subject will be found in their recent paper (28)   In all their cases the subjective and objective symptoms present in the spontaneous attacks could be duplicated by the application of pressure over the carotid sinus   By varying the intensity and duration of stimulation it was possible to induce with regularity the premonitory symptoms such as weakness, dizziness and even convulsions, without actually producing syncope   This condition, therefore, offered an unusual opportunity to study the relationship between these various manifestations, as well as the mechanism of syncope itself

In most of the patients studied by Weiss and Baker fainting was found to be caused either by a marked slowing of the ventricular rate with a consequent fall in blood pressure, or by a marked fall in blood pressure without significant slowing of the pulse, or by both They have suggested that the third type of fainting, which is not associated with any significant changes in the heart rate or the blood pressure, is the result of cerebral vasoconstriction which leads to anoxemia   This explanation was suggested because of the accompanying facial pallor and the fact that the vascular reactions of the face and meninges are known to be qualitatively alike (29) (30)

The frequency of this "cerebral" type of carotid sinus fainting has not been fully appreciated   For this reason and in order further to

clarify the mechanisms involved, we have conducted the present study primarily on patients having this type of syncope   In an effort to reach a better understanding of the mechanisms of fainting and convulsions in general, we have included observations in this report on a few patients having cardiac and vasomotor syncope of carotid sinus origin and also some observations on syncope due to other causes

Since beginning this investigation approximately 18 months ago we have studied 32 patients, not including those reported by Weiss and Baker   The patients all gave a history of spontaneous attacks of dizziness and fainting, and in each individual attacks identical in nature could be produced by pressure on the carotid sinus   We have observed a considerably larger group of patients with spontaneous syncope in which the carotid sinus played no etiological rôle, and likewise have seen many patients with marked slowing of the pulse and fall in blood pressure on carotid sinus stimulation, with or without syncope, who have not been included in this report   In at least 23 of the 32 cases included in this report the fainting was independent of the cardiac slowing, and the accompanying fall in blood pressure, when present, was not significant   In 7 patients[3] the attacks were of such frequency and had extended over such a long period of time that section of the carotid nerve was considered justifiable   We have studied 6 of these cases in considerable detail

METHOD OF INVESTIGATION

The patients were chosen from a group of subjects who entered the hospital complaining of attacks of dizziness and fainting   The spontaneous syncope and associated symptoms could be reproduced by the application of pressure over one or both carotid sinuses   Histories were taken with special regard to the chief complaint, previous local pathology in the neck and the state of the vegetative nervous system   Routine physical and laboratory examinations were made, including a seven-foot teleorontgenogram

The technique of applying pressure over the carotid sinus to secure maximal stimulation was found to require practice   Furthermore, the exact location of the carotid bifurcation varied in different indi-

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[3] Case 21, who was seen by one of the authors, was included through the courtesy of Dr J C White of the Massachusetts General Hospital

viduals from the level of the angle of the jaw to that of the lower border of the thyroid cartilage The bulbar dilatation at the bifurcation was first located It was then manipulated until it could be held firmly over the cervical spine, when fairly strong pressure with gentle massage was applied, using the spine as a support

Before and during the induced attacks the heart rate and cardiac changes were routinely registered by means of continuous electrocardiographic tracings The blood pressure was determined by the auscultatory method In a few cases mean pressures were recorded directly from the femoral artery, with the aid of a needle and mercury manometer system, and in others continuous blood pressure and pulse tracings were obtained from the hand by the method of Wiersma (31) (32) The readings obtained with the auscultatory method paralleled the direct ones fairly closely except when complete asystole occurred (fig 2) Changes in the cerebral circulation were studied by measuring the oxygen and carbon dioxide content of the jugular blood before and during the induction of fainting, and by determining the effect of carotid sinus pressure on the spinal fluid dynamics In addition, the blood flow in the internal jugular vein was determined with a Gibbs thermoelectric recorder (33) Changes in the respirations were also noted and in a few cases recorded on a smoked drum Fluoroscopic observations were made on the effect of stimulation of the sinus on the gastrointestinal canal The effect on venous pressure was measured in several cases by the direct method of Moritz and von Tabora (34) In a few patients the sensitivity of the sinus was tested by the intravenous administration of sodium cyanide (35) Control observations were made by occluding the carotid artery below the sensitive sinus and by pressing over various other points In addition, the sensitivity of the sinus was confirmed by novocainization, which abolished the induced reactions

The state of the vegetative nervous system was studied in each patient, not only by evaluating symptoms and physical signs, but also by observing the postural reaction of the circulation and the autonomic reflexes induced by eyeball pressure and esophageal distention The relation of fainting to posture was studied in most cases Weiss and Baker have shown that atropin abolished the cardiac slowing due to sinus stimulation and thereby prevented the attacks in

cases where this was the cause of syncope   Following the observation that atropin had no effect on the cerebral or on the vasomotor types of fainting, patients in whom marked bradycardia occurred were atropinized in order to separate the cardiac from the other two types of syncope   In cases where the carotid sinus sensitivity was associated with curable conditions, such as digitalis intoxication and dietary deficiency, the carotid sinus reaction was studied during and after recovery from such disorders   Finally, the effect of section of the sinus nerve was studied in 7 patients who were observed for periods varying in length up to one year following the operation   The criteria for the operation were based on the duration and severity of the symptoms and on the inability of the patients in the face of such symptoms to carry on their occupations   We have operated on several patients who, in addition to having a hyperactive carotid sinus reflex, showed evidence of severe vegetative neuroses, in order to determine not only the effect on the symptoms related to the carotid sinus but also the the effect on the unrelated neurotic symptoms

<div align="center">OBSERVATIONS</div>

<div align="center">*Clinical manifestations*</div>

The ages of the patients studied varied from 13 to 71 years, the average being 45 6 years, 20 were males and 12 females   The spontaneous attacks of fainting varied considerably, both in duration and in frequency   The fainting lasted from $\frac{1}{2}$ to 3 minutes and the patients usually recovered with no symptoms other than an occasional headache   In a few instances the spontaneous attacks lasted for as long as 15 minutes, this period including, however, such symptoms as mental confusion, amnesia, and hallucinosis   In such patients the induced attacks were shorter than the spontaneous ones but included the same symptoms   In many patients there was a definite aura consisting in dizziness, weakness, epigastric distress or spots before the eyes   These patients had learned to lie down in order to prevent fainting   In other cases the attacks came on suddenly and without warning   The symptom of dizziness was described as being a blurring of vision and a sense of generalized weakness but never as being true vertigo   The spontaneous and the induced aurae were

always identical in a given patient   There was no history of biting of the tongue or loss of sphincter control   Uniformly, fainting occurred while the patient was in the upright position, either sitting or standing, it almost never occurred while the patient was lying down   One woman noted that pressure on the side of her neck caused fainting, another that turning her head quickly to one side would do likewise, and still another that dizziness was induced by positions of the head that tended to put traction on the carotid artery and also when her coat collar pressed against the sensitive side   The one patient who had spontaneous dizziness in the horizontal position complained that it occurred only when he lay in a position that presumably caused pressure on the sensitive sinus   A history of such mechanical causes of sinus stimulation was unusual, however   In some cases a relationship seemed to exist between the onset of attacks and such factors as emotional upsets, worry, fatigue and menstruation   Otherwise no precipitating causes for the attacks could be elicited   On recovery from the syncope none of the patients had the sensation of "well being" or of "relief" that is sometimes experienced after epileptic fits

Many patients gave clinical evidence of unstable vasomotor systems   In these patients such symptoms as palpitation, moist palms, emotional instability, skin sensitivity and nervousness were usually elicited   The evidence was further strengthened on physical examination   The heart rate was frequently unstable   The blood pressure level tended to fluctuate spontaneously over a considerable range   Many patients had a persistently low basal metabolic rate   In the entire group it varied from plus 15 to minus 25 per cent and was lowest in those patients who showed clinical evidence of having the most severe and widespread neurotic manifestations   Dermatographia and various other neurogenic skin lesions were sometimes noted   The electrical resistance of the skin of the forearms and legs as estimated by the electrocardiograph was usually high   Evidence suggestive of local changes in the sensitive carotid sinus was noted in many cases   Thus a bulbar dilatation could often be palpated at the carotid bifurcation and in the older patients there was evidence of local sclerotic changes

Various functional and organic disorders were associated with the hyperactive reflex in most of our patients   Sixteen were emotion-

ally unstable and of this group, 3 were considered to have a severe vegetative neurosis Ten had either hypertension or arteriosclerosis, 5 showed clinical evidence of mild coronary heart disease and 9 had either histories or physical signs of enlarged lymph nodes on the sensitive side There were also 5 patients with duodenal ulcer demonstrable by X-ray, 4 with syphilis of the central nervous system, 3 with evidence of digitalis intoxication; 3 with pronounced dietary deficiency, and 1 with congenital dextroposition of the aorta and dysphagia lusoria

Induced attacks

Pressure over the right or left carotid sinus resulted in symptoms identical with the spontaneous attacks Depending on the degree and duration of pressure, the symptoms consisted in faintness and pallor of the face, followed by unconsciousness and, in most cases, by convulsive twitchings which usually began on the contralateral side and then became generalized Although unconsciousness usually just preceded or occurred simultaneously with the convulsions, in many cases the latter appeared before actual syncope Indeed, in several instances severe generalized convulsions were induced by the application of pressure on the carotid sinus without having the patient lose consciousness Numbness and tingling of the extremities were prominent symptoms, usually starting in the contralateral extremities and spreading to the whole body before actual fainting occurred Other symptoms frequently present were loss of vision, nausea and epigastric distress Dilatation of the ipsolateral pupil, strabismus, lacrimation, momentary loss of memory, states resembling catalepsy and sleep, and emotional changes were occasionally observed, and in 2 patients the Babinski sign became positive during syncope Case 25, an alcoholic patient who had frequent hallucinations before entry, developed identical hallucinations lasting for several minutes during recovery from induced syncope This was repeatedly observed over a period of several days Likewise, in case 28 a Parkinsonian tremor was brought out for a few minutes following sinus stimulation Both these cases, however, had prolonged cardiac asystole and such exacerbation of symptoms was obviously related to the cerebral ischemia accompanying the asystole

rather than to a specific carotid sinus reflex pathway to the brain
During pressure a change in the character of respirations was usually
noted (fig 1) The breathing became somewhat deeper and more
labored, similar to that sometimes observed in patients during spon-
taneous syncope and sleep In a few instances with maximal effect
it resembled that seen in orthopnea The intensity of respiratory
responses seemed to be unrelated to the tendency to faint

Depending on the intensity of the stimulus, we could often induce
unconscious states of different degrees The onset and depth of un-
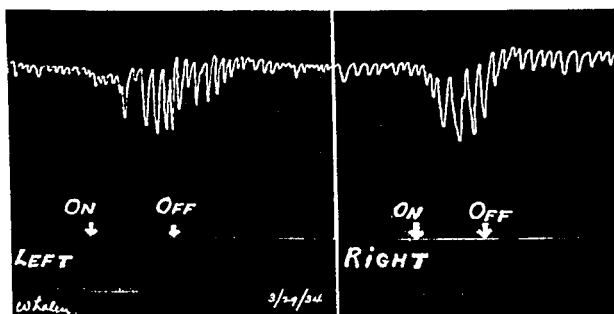consciousness could be influenced through other external stimuli and

FIG 1 RESPIRATORY RESPONSE TO CAROTID SINUS PRESSURE IN CASE 31

through certain types of cerebral activity In cases 1, 3 and 10 nu-
merous comparative observations revealed that noise, light, pain,
fear and excitement delayed the onset and partially or completely
counteracted the efficacy of the stimuli from the carotid sinus In
several patients unconsciousness was preceded by such manifestations
as closure of the eyes, loss of ability to move the extremities, help-
lessness and motor collapse as the result of complete loss of muscular
tone, inability to speak, mental confusion and indefinite trance-like
sensations Several patients felt as though they were "going to
sleep" as they approached the unconscious state Many patients
were mentally confused as consciousness returned Occasionally
such symptoms almost instantaneously followed the application of

pressure   In these respects there was a certain degree of similarity between the manifestations of the unconscious state of cerebral syncope and that of deep natural sleep

Fainting was induced by the application of pressure over the right sinus alone in 13 cases, over the left in 11 cases and over either sinus in 8 cases   In some patients with unilateral sinus fainting, stimulation of the opposite sinus failed to produce symptoms, while in others it induced symptoms of varying severity   The duration of pressure necessary to produce unconsciousness varied from 4 to 40 seconds but was fairly constant in a given individual   In all cases fainting could be induced much more rapidly when the patient was in the upright than in the horizontal position   Simple occlusion of the carotid artery well below the sinus never induced unconsciousness or convulsions, although in several patients with very sensitive sinuses such occlusion, if accompanied by massage, did induce mild symptoms   In cases 20 and 21 simple occlusion of the artery was without effect, immediately following release of the artery, however, symptoms were momentarily induced, apparently as the result of a sudden increase in intrasinal pressure

Some of the manifestations of the cerebral type of syncope in man are similar to those observed by Koch in animals (36)   Koch observed that in dogs recovering from the effect of anesthesia, stimulation of the carotid sinus induces instantaneous stoppage of muscular movements   The head and tail of the animal hang more and more limply until finally the animal "lies as if in sleep "

Heart rate and electrocardiographic findings

In 6 of the patients (cases 24 to 29 inclusive) the degree of cardiac slowing was sufficient to cause the fainting that ensued on carotid sinus stimulation   This fact is clear in cases 24, 25, 26 and 28, in which fainting could not be induced when the cardiac slowing was abolished by the administration of atropin   In the other 2 patients the degree of cardiac slowing was so marked that it was assumed to be the cause of fainting

In the 26 remaining cases, although varying degrees of cardiac slowing did occur, it could be definitely established that such slowing was not the cause of syncope   In many cases the slowing was either

absent or of too slight a degree to cause fainting   In these cases,
as well as in the remaining ones where the cardiac slowing was more
marked, the administration of atropin did not prevent the fainting
reaction although it abolished the reflex slowing   Further evidence
that fainting in these cases was not the result of cardiac slowing is
afforded by observations made on case 2 where the slowing was very
marked   Denervation of the sinus abolished the induced fainting
reaction without altering the degree of reflex slowing   In case 3,
although syncope could be induced only when the left sinus was
stimulated, the most marked cardiac slowing occurred when the right
sinus was stimulated   It can be noted in table I that, in many cases,
although the slowing was quite marked immediately following sinus
stimulation, it was temporary and the rate had approached normal
long before actual fainting occurred

Because most of the patients included in this study were those with
a predominating cerebral type of reflex, the electrocardiographic
changes were not very striking except in the 6 patients in whom syn-
cope was of cardiac origin   This phase of the subject has been tho-
roughly discussed by Nathanson (37) (38), by Weiss and Baker (28)
and by Sigler (39)   The principal effect of carotid sinus stimulation
was a slowing of the ventricular rate as a result of depression of either
the sinoauricular or the auriculoventricular nodes   Cases 4, 5 and
10, however, actually showed a slightly increased heart rate, and in
cases 17, 20 and 23 there was no change   Varying degrees of slowing
were noted in the remainder of the patients, the most marked changes
occurring in the 6 cases of cardiac syncope   Such slowing was always
accompanied by a depression of the S-A node and in 10 cases there
was, in addition, a depression of the A-V node   The S-A nodal effect
varied from a very slight slowing of the auricular rate to a complete
suppression of the P wave for the duration of stimulation   During
auricular standstill there was often ventricular escape from varying
foci   In 9 cases ectopic auricular contractions occurred and were
followed by normal ventricular complexes   The most marked P
wave changes were seen in lead 3   When A-V block occurred it was
usually complete for several auricular contractions, in a few cases
the effect was manifested only by an increase in the P-R interval
An analysis of the several electrocardiographic tracings that were

TABLE I

#	Patient	Age	Carotid sinus	Blood pressure Before pressure mm Hg	Blood pressure During pressure mm Hg	Heart rate Before pressure	Heart rate During pressure Initial	Heart rate During pressure Average	Pallor of face	Hyperpnea	Dizziness	Fainting	Convulsions	Effect of atropin on symptoms	Primary sinus reflex	Additional diagnosis
1	J D	42	Right	120/70	90/?	67	37	50	+	+	+	+	+	None	Cerebral	Duodenal ulcer, severe neurosis
			Left	120/70	70/?	73	60	65	+	+	+	0	+	None	Cerebral	
2	B F	60	Right	156/85	90/50	71	15	38	+	+	+	+	0	—	Cerebral	Arteriosclerotic heart disease
			Left	156/85	105/74	81	38	48	+	+	+	0	0	—	Cerebral	
3	R R	17	Right	120/70	85/40	70	22	54	0	0	+	0	0	None	Cardiac	Seborrhea, acne
			Left	120/70	126/80	75	63	71	+	?	⊘	+	+	None	Cerebral	
4	M H	13	Right	130/80	130/80	100	120	120	0	+	+	+	+	—	Cerebral	Chronic tonsillitis
			Left	130/80	130/80	77	77	77	0	⊘	⊘	⊘	⊘	—	—	
5	E M	32	Right	126/90	132/90	77	86	86	0	+	+	+	0	—	Cerebral	Dermatographia
			Left	126/90	126/90	71	86	86	+	+	+	+	0	—	Cerebral	
6	D M	46	Right	150/100	140/100	83	75	75	+	+	+	0	+	None	Cerebral	Neurosis, mild hypertension
			Left	140/100	120/80	75	55	55	+	+	+	+	+	None	Cerebral	
7	A F	45	Right	128/78	128/78	60	15	40	?	+	+	0	+	—	Cerebral	Neurosis, mild hypertension
			Left	128/78	128/78	60	37	48	?	+	+	+	+	—	Cerebral	
8	A H	40	Right	155/90	140/80	100	60	86	+	+	+	0	+	—	Cerebral	Dental abscesses, mild hypertension
			Left	144/86	144/86	91	88	88	+	?	+	+	+	—	Cerebral	

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No.		Age	Side	BP 1	BP 2											Diagnosis
9	J H	23	Right	112/80	106/60	72	50	60	+	+	+	+	+	—	Cerebral	Neurosis
			Left	120/80	110/70	72	72	72	o	o	o	o	o	—	Cerebral	
10	E F	13	Right	125/70	125/70	83	93	93	+	+	+	+	+	—	Cerebral	Bilateral tuberculous cervical adenitis, severe neurosis
			Left	125/70	125/70	75	65	68	+	+	+	+	+	—	Cerebral	
11	L P	45	Right	130/80	130/80	100	100	100	o	o	+	+	+	None	Cerebral	Chronic alcoholism, dietary deficiency, pellagra
			Left	130/80	130/80	100	65	79	o	+	+	+	+	None	Cerebral	
12	M C	63	Right	146/90	128/80	75	60	64	o	+	+	+	+	None	Cerebral	Hypertension, arteriosclerosis
			Left	146/90	108/?	75	60	64	o	o	+	+	+	None	Cerebral	
13	J C	59	Right	132/70	90/?	56	37	42	+	+	+	+	+	None	Cerebral	Duodenal ulcer, spastic constipation
			Left	140/70	110/?	56	45	50	+	o	+	+	+	None	Cerebral	
14	E Q	24	Right	120/56	84/30	100	17	37	+	+	+	+	+	Diminished	Cerebral	Mentally subnormal, severe neurosis
			Left	120/70	100/54	80	30	37	+	o	o	?	?	Diminished	Cerebral	
15	J L	61	Right	138/76	88/50	86	21	67	+	+	+	o	o	None	Cerebral	Tabes dorsalis
			Left	130/74	90/48	83	18	64	o	o	o	+	+	None	Cerebral	
16	A D	63	Right	140/76	140/76	68	68	68	o	o	o	o	o	—	Cerebral	Lymphosarcoma, arteriosclerosis
			Left	124/80	98/?	66	60	62	+	+	+	+	+	—	Cerebral	
17	R S	71	Right	130/70	106/?	75	75	75	o	+	+	+	+	None	Cerebral	Peptic ulcer, neurosis, dietary deficiency
			Left	130/70	110/?	75	75	75	o	o	+	+	+	None	Cerebral	
18	F F	46	Right	145/80	145/80	75	64	66	o	o	o	o	o	None	—	Hypertension, hypertensive heart disease
			Left	145/80	100/?	75	12	30	+	+	+	+	+	None	Cerebral	
19	L B	43	Right	148/90	88/56	71	15	48	+	+	+	+	+	—	?	
			Left	126/80	100/70	68	30	45	+	+	+	+	+	—	Cerebral	

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TABLE I—*Concluded*

PATIENT	AGE	CAROTID SINUS	BLOOD PRESSURE Before pressure mm Hg	During pressure mm Hg	HEART RATE PER MINUTE Before pressure	During pressure Initial	Average	Pallor of face	Hyperpnea	Dizziness	Fainting	Convulsions	EFFECT OF ATROPIN ON SYMPTOMS	PRIMARY SINUS REFLEX	ADDITIONAL DIAGNOSIS
20 C D	36	Right	120/80	120/80	79	70	76	0	?	+	0	0	—	—	Dextroposition of aorta
		Left	120/80	100/84	78	78	78	0	?	+	0	0	None	Cerebral	
21 S G*	62	Right	140/80	120/70	100	65	70	+	+	+	+	+	—	Cerebral	Neurosis, duodenal ulcer
		Left	140/80	90/50	80	30	?40	+	+	+	+	+	—	Cardiac	
22 A R	57	Right	198/100	180/90	100	65	80	+	+	+	+	0	—	Cerebral	Hypertension, moderate cervical kyphosis, healed pulmonary tuberculosis
		Left	200/90	170/80	100	60	75	+	+	+	+	0	—	Cerebral	
23 M K	42	Right	165/105	165/105	90	90	90	+	+	+	0	+	—	Cerebral	Neurosis, mild hypertension
		Left	185/95	175/?	80	90	90	0	+	+	0	0	—	Cerebral	
24 S M	46	Right	135/80	80/?	82	60	60	0	+	+	0	0	—	—	Adenoma of thyroid, menopause
		Left	120/80	90/?	68	24	46	+	+	+	+	+	Diminished	Cardiac	
25 P M	38	Right	134/90	85/65	85	10	10	+	?	+	?	+	Abolished	Cardiac	Chronic alcoholism, delirium tremens, pellagra
		Left	138/94	85/65	80	6	6	+	?	+	+	+	Abolished	Cardiac	
26 D K	66	Right	140/95	80/50	79	20	36	+	+	+	+	+	Diminished	Cardiac	Polycythemia vera, hypertension, fistula in ano
		Left	140/95	100/70	79	30	43	+	+	+	0	0	Diminished	Cardiac	

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No.		Age	Side	BP												Diagnosis
27	A R	54	Right	160/96	94/60	100	10	37	+	?	+	+	0	—	Cardiac	Infectious arthritis
			Left	142/90	116/66	100	40	71	0	0	0	0	0	—	—	
28	L L	55	Right	150/90	Too low to read	75	5	5	+	+	+	+	+	Abolished	Cardiac	Hypertension, pyelonephritis, tabes dorsalis
29	C M	56	Right	140/80	?	60	10	30	+	+	+	+	+	Abolished	Cardiac	Neurosis
			Left	140/86	?	60	10	24	+	+	+	+	+	—	Cardiac	
30	M L	44	Right	124/76	80/56	115	88	91	?	+	+	+	+	—	Vasomotor	Tabes dorsalis, mild postural hypotension
			Left	126/76	80/50	107	93	95	?	+	0	+	0	—	?	
31	J W	48	Right	130/70	90/60	94	32	50	+	+	+	+	+	—	?	?Coronary thrombosis, duodenal ulcer, neurosis
			Left	130/70	90/50	80	40	53	?	+	+	0	+	—	—	
32	G E	57	Right	No change	No change			No change	0	0	0	+	0	—	—	Neurosis
			Left	Marked fall	Moderate slowing				+	?	+	0	0	—	?	

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* Dr J C White of the Massachusetts General Hospital kindly allowed us to include this case

taken from each of these patients has revealed no predominance of S-A or A-V depression from stimulation of either the right or the left carotid sinus, for example, A-V block was induced as frequently from stimulation of one sinus as from the other   Frequently, however, in a given patient pressure on one sinus induced A-V block whereas pressure on the other induced only a depression of the S-A node

Blood pressure

The cerebral type of syncope was usually accompanied by a moderate fall in blood pressure   This was due partly to the accompanying bradycardia and partly to a vasomotor depressor reaction induced reflexly from the carotid sinus (note especially cases 1, 12, 13, 16 and 17)   These two factors were readily separated by the use of atropin, which abolished the cardiac slowing but had no effect on the depressor reflex

In the 6 patients with cardiac syncope there was a marked depression of the blood pressure which was largely the result of cardiac slowing   In case 30 a marked vasomotor depression of the blood pressure occurred on carotid sinus stimulation and this depression was maintained long enough to cause symptoms

In the remainder of the patients the induced fainting was not the result of a fall in the blood pressure   In the majority of this group the changes in blood pressure depended entirely on the degree of cardiac slowing and were abolished by atropin without altering the tendency to faint   In several cases the blood pressure actually rose during sinus stimulation and in most cases the fall was insufficient to produce symptoms   In cases 1 and 2, where there was a marked fall in blood pressure, section of the sinus nerve abolished the induced fainting but did not alter the depressor reaction (fig 2)   In cases 3 and 21, only minor symptoms occurred upon stimulation of that sinus which induced the greatest fall in blood pressure   Furthermore, in several patients in whom a marked initial depression occurred, direct arterial pressure tracings showed that the blood pressure had actually risen to its initial level before the patients became unconscious (fig 2)   Such findings clearly demonstrate that in most of our cases the fall in blood pressure is not the cause of symptoms   The various types of blood pressure changes obtained by the Wiersma
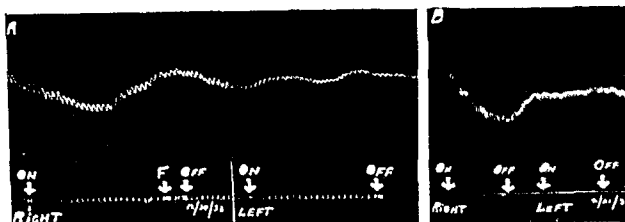
FIG 2 BLOOD PRESSURE TRACINGS OBTAINED BY DIRECT CANNULATION OF THE
FEMORAL ARTERY IN CASE 1

The legends "on" and "off" indicate respectively stimulation and release of the carotid
sinus   Tracing A was obtained before operation and tracing B after operation   Note
that a depressor response was obtained only from the right carotid sinus and that the
same response occurred after operation when symptoms were not present   The initial
mean blood pressure in tracing A is 100 mm Hg and at the lowest point 76 mm Hg
Auscultatory blood pressure readings at these points were 120/80 and 90/60 respectively
The letter F in tracing A indicates the point at which the patient fainted
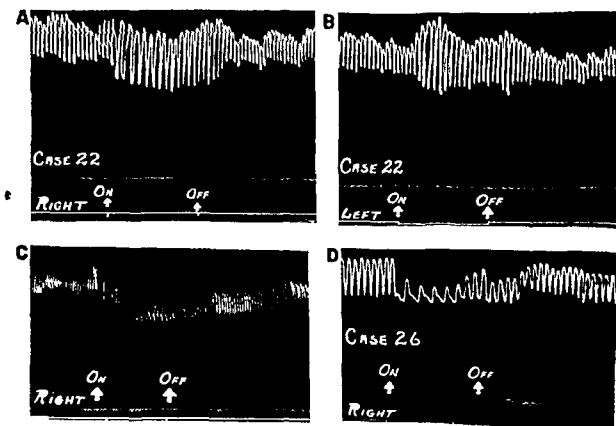
FIG 3 TYPES OF BLOOD PRESSURE AND PULSE CHANGES DUE TO CAROTID
SINUS PRESSURE RECORDED FROM THE HAND BY THE METHOD OF
WIERSMA

The legends "on" and "off" indicate the beginning and termination of sinus pressure
Note that changes can occur not only in the mean arterial pressure but also in both the
systolic and diastolic levels separately   Tracing A shows principally a fall in diastolic
pressure, B a rise in the systolic and a fall in the diastolic, C a fall in the mean pressure
and D a fall in systolic pressure alone

technique are shown in figure 3   These tracings demonstrate not only the changes that occur in mean arterial blood pressure but also those that may occur in systolic, diastolic and pulse pressures   The variations result from different combinations of such factors as cardiac slowing, vasomotor changes and possibly cardiac output

The greatest depression in blood pressure was noted in patients with hypertension   In individual patients the level to which the blood pressure fell was quite constant and was not related to changes in initial level   In hypertensive patients with unstable blood pressures (cases 2 and 26) initial carotid sinus stimulation tended to induce a lower blood pressure level, which was maintained for periods of time varying up to one hour

Venous pressure

The pressure in the femoral vein was continuously recorded during the induced attacks in 3 patients having the cerebral type of syncope   No significant change was noted

Facial pallor

The cerebral type of fainting was nearly always accompanied by marked initial pallor of the face, followed by intense flushing on release of pressure   In a few instances such pallor did not occur and in several cases flushing of the face occurred before release of pressure   The intensity of pallor did not always parallel the tendency to faint and was independent of the fall in blood pressure or change in heart rate   The pallor which accompanied cardiac syncope was not always abolished by atropin, a fact which suggests that some direct cerebral vasoconstriction took place in these cases, too

Spinal fluid dynamics

The spinal fluid pressure and the height of the pulse oscillations were observed during fainting in 10 cases   Where fainting was of the cerebral type and was associated with pallor of the face which was followed, on release of pressure, by marked flushing, the results were clear cut and striking   Coincident with stimulation of the carotid sinus the spinal fluid pressure remained at its initial level or fell from 10 to 30 mm of water and the pulse oscillations diminished

greatly in amplitude, in some instances disappearing entirely On release of pressure and coincident with flushing of the face, the spinal fluid pressure rose characteristically from 20 to 150 mm of water and the amplitude of the pulse oscillations increased to several times the normal On reaching a maximal level the spinal fluid pressure returned fairly promptly to the initial level (fig 4) These observations were made several times in each of the above cases Although these changes closely paralleled the degree of facial pallor, they did
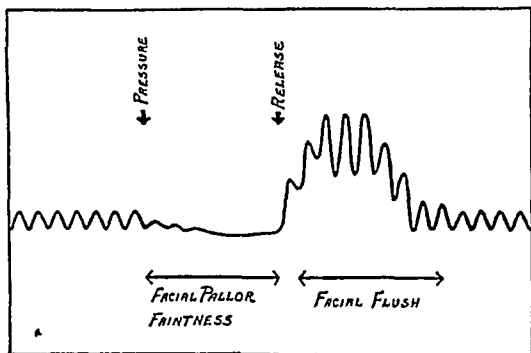
FIG 4 A SCHEMATIC TRACING REPRESENTING THE CHANGES IN SPINAL FLUID PRESSURE AND PULSE OSCILLATIONS DURING AND AFTER CAROTID SINUS PRESSURE

Note the disappearance of pulse oscillations and slight diminution of pressure during stimulation and the sharp rise in pressure and increase in pulse oscillations on release of pressure

not always parallel the tendency to faint In 6 control patients without spontaneous and induced fainting or pallor there was either no change in the spinal fluid pressure and pulse oscillations, or else the pressure rose at the time of sinus stimulation, as a result of jugular compression, and fell upon release In several of these control patients there was slight slowing of the pulse with coincident fall in blood pressure These typical findings noted in the cerebral type of fainting suggest some alteration in the cerebral vasomotor system during the fainting which parallels the pallor and flushing of the face In none of these cases was the bradycardia or fall in blood pressure sufficient to account for the spinal fluid changes

Cerebral blood flow

In order to estimate changes in cerebral blood flow, the oxygen tension of the blood from the internal jugular vein was determined on the side opposite the sensitive sinus   Samples were taken before sinus stimulation and during actual fainting   In order to control the changes due to compression of the carotid artery the initial samples were taken while the opposite carotid artery was occluded

TABLE II

Changes in blood gases during induced syncope

CASE NUMBER		ARTERIAL BLOOD		INTERNAL JUGULAR BLOOD		A-V O₂ DIFFER-ENCE	TYPE OF SYNCOPE
		O₂ content	O₂ satura-tion	O₂ content	O₂ satura-tion		
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	
1	Control	19 10	92 1	13 04	62 8	6 06	Cerebral
	During syncope			11 60	55 9	7 50	
4	Control	16 15*	95 0	10 65	62 8	5 50	Cerebral
	During syncope			11 17	63 6	4 98	
5	Control	18 33*	95 0	12 16	63 1	6 17	Cerebral
	During syncope			12 90	67 0	5 43	
15	Control	15 70	94 2	10 38	62 2	5 32	Cerebral
	During syncope			10 12	60 7	5 58	
28	Control	15 58*	95 0	10 17	62 0	5 41	Cardiac
	During syncope			4 05	25 0	11 53	

* These figures are based on the assumption that the arterial saturation was 95 volumes per cent.

below the sinus   The results are summarized in table II   In the 4 patients who exhibited the cerebral type of fainting the changes were insignificant   The minor decrease in blood flow noted in cases 1 and 15 is probably due to the slight cardiac slowing which was present in these cases   In case 28, in which fainting was the result of cardiac asystole, a very marked decrease in the venous oxygen tension and a marked increase in the arteriovenous oxygen difference were noted
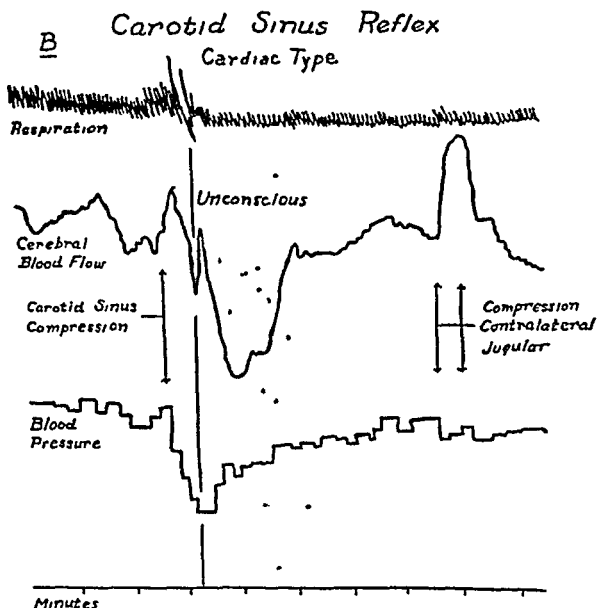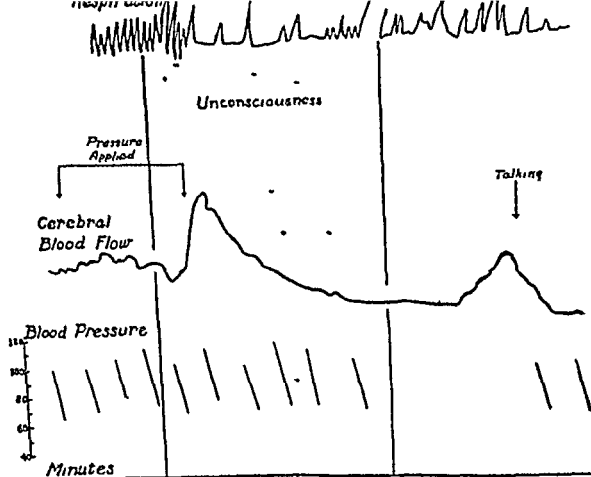
FIG 5 THE CEREBRAL BLOOD FLOW AS RECORDED FROM THE INTERNAL JUGULAR
VEIN BY MEANS OF A GIBBS THERMOELECTRIC RECORDER

Tracing *A* was obtained from case 1, who had the cerebral type of fainting   Tracing *B*
was from a patient with fainting due to cardiac asystole   Note that the cerebral blood
flow actually increased during unconsciousness in the patient with cerebral fainting, and
diminished greatly during unconsciousness due to cardiac asystole

The blood flow from the internal jugular vein was also determined by means of a Gibbs thermoelectric recorder   The thermocouple was placed in the internal jugular vein opposite the sensitive sinus and a continuous tracing obtained, showing the level of blood flow before, during and after syncope [4]   In case 1, where the fainting was of the cerebral type, no significant change in the blood flow was noted   In a patient who fainted because of cardiac asystole, a marked decrease in the cerebral blood flow was noted by this method (fig 5)

It is therefore clear that the changes in total cerebral blood flow in the group of patients with cerebral syncope are insignificant   The slight changes can be accounted for by minor variations that occurred in the heart rate   It has previously been shown that when fainting is the result of cardiac asystole the cerebral blood flow is greatly diminished (28)

Respirations

Upon the application of pressure over the sensitive carotid sinus the character of the respirations usually changed   The breathing tended to become deep and labored, and when the effect was marked all the accessory muscles of respiration were brought into action   The more marked changes were noted in the older patients, and in 2 patients who suffered from attacks of paroxysmal dyspnea the respiratory reaction simulated the spontaneous dyspnea   This reaction seemed to be an associated reflex, independent of cardiac slowing and of general changes incident to fainting   It was not abolished by atropin   In cases 28 and 31, in which it accompanied cardiac fainting, atropin and adrenalin abolished the fainting and cardiac slowing but had no effect on the respiratory reaction   Often the respiratory effect, under the influence of these drugs, was actually accentuated, presumably because stimulation could be maintained for a longer time without the induction of syncope

Effect of posture

In all cases the tendency to faint was definitely related to posture, in spite of the fact that the fainting did not depend on changes in the

[4] We are indebted to Dr and Mrs F A Gibbs and to Dr William G Lennox for these observations

systemic circulation   Fainting could be induced most rapidly with the patient in the standing position, next in the upright sitting position and less easily as the horizontal position was approached   Occasionally fainting was easily induced in the upright but could not be induced in the horizontal position   Such findings suggested that these patients might react abnormally to posture alone   This, however, was not the case, as postural hypotension could not be demonstrated, and conversely, although 1 patient with postural hypotension did exhibit a sensitive carotid sinus, 3 others observed by us had no increased sensitivity whatsoever   In addition, patients 1 and 3 were placed on a tilting table and elevated to 80 degrees above the horizontal   Fainting could be induced by this method (16) only after the administration of $1\frac{1}{2}$ grains of sodium nitrite   This reaction is similar to that of normal individuals (40)   Furthermore, similar observations following section of the carotid nerve demonstrated no change in the postural reaction (chart 1)   These experiments suggest the lack of direct relationship between postural fainting and fainting due to stimulation of the carotid sinus

Gastrointestinal manifestations

Several individuals experienced nausea and patients 13 and 24 actually vomited following pressure over the sinus   In case 13 this was very marked when the left sinus was stimulated, although fainting could be induced only from the opposite side   Fluoroscopic studies on this patient revealed reverse peristaltic waves in the stomach, coinciding with the nausea   Similar findings have been reported by Danielopolu (41)

Effect of drugs

The effect of drugs which have fairly well known specific effects on portions of the nervous and circulatory systems has been ascertained in an effort to obtain a better understanding of the mechanisms and clinical manifestations involved in this syndrome

1 *Atropin*   Weiss and Baker have shown that atropin in sufficient doses abolishes fainting when it results from cardiac asystole, but has no effect when the fainting is caused by a primary fall in blood pressure   The explanation of this difference in the effect of atropin

on these two types of fainting lies in the fact that the asystole is of vagal origin, while the primary depression of the blood pressure results from sympathetic rather than from vagal impulses   In our cases of "cerebral" fainting, atropin in doses as high as 7 0 mgm
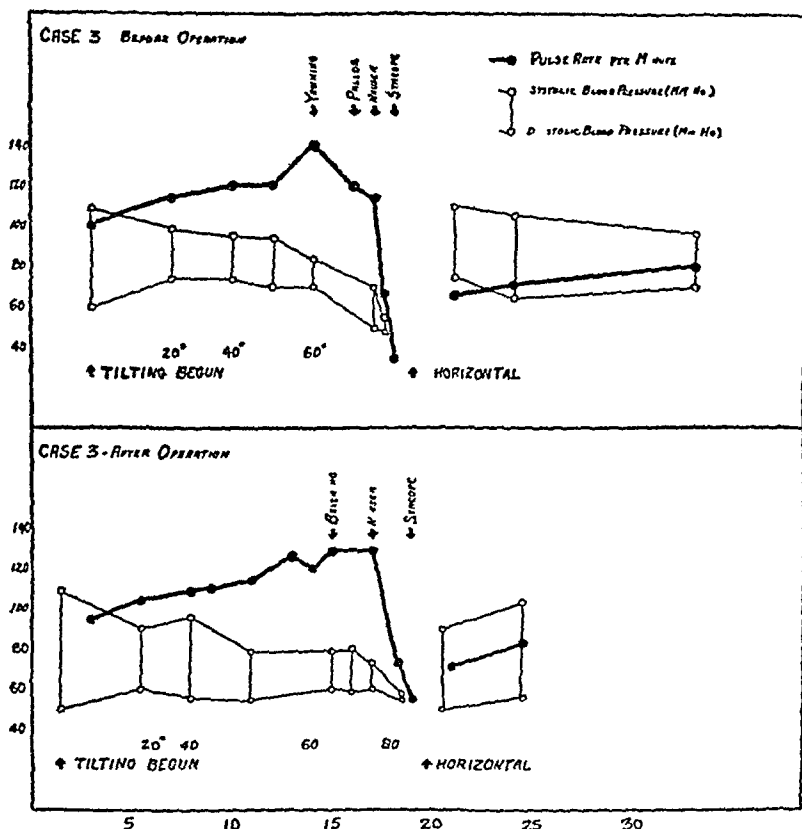

CHART 1   CHANGES IN THE HEART RATE AND BLOOD PRESSURE ASSOCIATED WITH POSTURAL FAINTING INDUCED BY MEANS OF A TILTING TABLE

The two charts represent this reaction in case 3, before and after operation   The reaction was similar on both occasions and fainting occurred at approximately the same time   In each instance the patient was given 1½ gr sodium nitrite orally before the experiment was begun   The ordinate represents the blood pressure in mm Hg and the heart rate in beats per minute, the abscissa the time in minutes

subcutaneously failed to abolish the fainting and convulsions, although 2 0 mgm was found to be sufficient to abolish most of the cardiac slowing.   Whether administered subcutaneously, intramuscularly or intravenously, atropin has given identical results   In cases 1, 2, 7, 14, 15 and 18, where fainting was associated with rather

marked cardiac slowing, this drug abolished the slowing but had no effect on the fainting   In cases 24, 25, 26 and 28 it prevented the fainting as well as the cardiac slowing   In cases in which there was enough slowing to cause doubt as to the type of carotid sinus reflex present, we have therefore given atropin in order to differentiate the cerebral and vasomotor types from the vagal   In cases with cardiac slowing this drug abolished the fall in blood pressure due to such slowing, but some depressor effect often remained, indicating that the fall in blood pressure was due to two separate mechanisms   These results are tabulated in table I

2 *Pilocarpin*   Pilocarpin in doses sufficient to cause systemic symptoms and signs of parasympathetic stimulation, such as salivation, sweating and increased gastrointestinal motility, had no effect on the symptoms produced by carotid sinus stimulation in cases 1 and 3

3 *Epinephrin*   Epinephrin raises the blood pressure and the heart rate, increases the systemic blood flow, and, as was also noted by Weiss and Baker, abolishes the cardiac and vasomotor types of syncope   It was therefore somewhat surprising to find that it failed to prevent the cerebral type of fainting

In our cases of cardiac syncope, in which epinephrin was administered, it abolished the fainting   It did so by exerting a local stimulating effect on the heart, thereby inducing an idioventricular rhythm fast enough to prevent cerebral anoxemia   It had, on the other hand, no effect on the afferent or efferent nervous pathways   This was indicated by the fact that when either sinus or A-V block occurred in control observations it still persisted after adequate doses of epinephrin   In previous studies (14) on a patient with vago-vagal syncope we have demonstrated that both epinephrin and ephedrin acted in this manner in preventing reflex Adams-Stokes' attacks

4 *Ephedrin*   The effect of ephedrin was studied because, in addition to its adrenalin-like action, it also has a marked stimulating effect on certain autonomic centers   Furthermore, a prolonged action can be obtained by administering it orally   This drug was given orally or intravenously in doses sufficient to produce systemic effects, it failed, however, to have any influence on the reaction in patients who suffered from the cerebral type of fainting (cases 10, 13, 20 and

23)   In patients with cardiac asystole its effect was similar to but less marked than that of adrenalin   Our experience concerning the effect of both adrenalin and ephedrin in such cases of reflex cardiac asystole indicates that for a given dose of either drug the response of the ventricle, as indicated by the rate and rhythm of the idio-ventricular beats, depends on the degree of myocardial disease present

5 *Strychnin*   Strychnin decreases the threshold of impulses at the synapses and Heymans (42) has found that it increases the carotid sinus sensitivity in animals   Two milligrams administered intramuscularly in cases 1 and 23 had no apparent effect on the carotid sinus reflex

6 *Acetyl-β-methylcholin*   Since this drug stimulates the para-sympathetic nervous system and dilates the peripheral vessels (43) (44), the possibility that it might influence the cerebral type of faint-ing was considered   It was given subcutaneously to cases 1 and 23 and no alteration in the sinus reflex was noted although the systemic effect on the patients was marked   In case 24, where the symptoms were largely cardiac in origin, this drug, through its vagal effect, increased the degree of cardiac slowing, thus increasing the tendency to faint

7 *Amyl nitrite*   Since this drug is a peripheral vasodilator (40), its effect was studied because of the possibility that it might influence the cerebral blood flow through regional vasodilatation   The carotid sinus was stimulated during the inhalation of this substance in cases 1, 2, and 3, but no definite change in the fainting reaction was ob-served

8 *Carbon dioxide and oxygen*   Several workers (45) (46) (47) have stated that carbon dioxide has a sensitizing effect on the carotid sinus in animals   Furthermore, there is evidence that carbon dioxide dilates the cerebral vessels (48) and can strikingly influence the cere-bral reactions in certain psychoses   In cases 1, 3, and 15 we adminis-tered 10 per cent carbon dioxide in oxygen by inhalation until marked hyperpnea and flushing of the skin occurred   Even at the height of symptoms and while the inhalation was still being carried on, no change in the sinus reaction was noted   Arterial and venous blood samples during this procedure showed definite increases in the carbon dioxide content

Voluntary hyperventilation and inhalation of pure oxygen over long periods of time likewise produced no change in the fainting reaction in cases 1 and 3   The latter finding suggests that anoxemia may not have played a major causative role
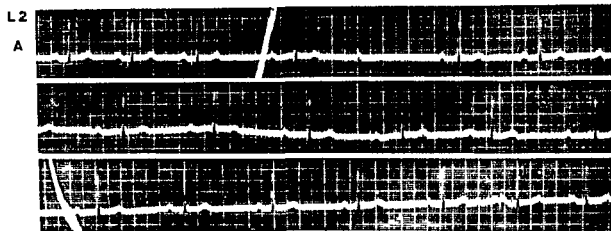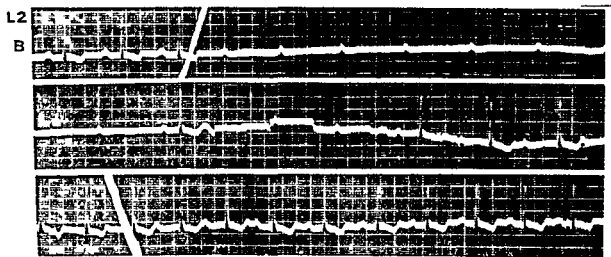

Fic 6 Continuous Electrocardiogram during Left Carotid Sinus Pressure in Case 18, before the Administration of Digitalis

The white marks on the upper and lower tracings represent respectively the beginning and release of pressure   There is one dropped beat due to A V block and a maximum change in the P R interval of from 0 26 to 0 4 second

Fig 7 Continuous Electrocardiogram during Carotid Sinus Pressure in Case 18 after the Administration of 27 gr Digitalis

The white marks in the upper and lower tracings represent respectively the beginning and the end of pressure on the sinus   Note the prolonged ventricular asystole due to A V block as contrasted with figure 6   The T waves show the digitalis effect

9 *Ergotamin*   Ergotamin in small doses is a powerful sympathetic stimulant, in large doses, on the other hand, it paralyzes certain types of sympathetic nerve endings   The amount which can safely be administered to man can hardly exert such a depressant effect

on the sympathetic endings   We have often observed, on the contrary, an elevation of both the systolic and the diastolic blood pressure following the subcutaneous administration of from 0 5 to 1 0 mgm   Ergotamin tartrate given intramuscularly in doses of from 0 5 to 1 0 mgm` did not appreciably alter the fainting reaction in cases 6 and 16

TABLE III

Effect of digitalis on cerebral and cardiac syncope

CASE NUMBER		NORMAL HEART RATE PER MINUTE	RIGHT SINUS		LEFT SINUS	
			Duration of pressure required to produce fainting	Longest ventricular pause	Duration of pressure required to produce fainting	Longest ventricular pause
18	Control	74	No fainting	0 9 sec (rate 64)	21 sec	5 3 sec
	Digitalis (27 gr)	86	40 sec	2 5 sec	10 sec	8 5 sec
6	Control	80	No fainting	0 8 sec (rate 75)	20 sec	1 1 sec (rate 55)
	Digitalis (40 gr)	100	14 sec	0 6 sec (rate 100)	9 sec	1 1 sec (rate 55)
16	Control	66	No fainting	0 9 sec (rate 66)	30 sec	1 0 sec (rate 60)
	Digitalis (42 gr)	60	No fainting*	1 0 sec (rate 60)	15 sec	1 1 sec (rate 55)
26	Control	65	14 sec	5 0 sec	No fainting	2 0 sec (rate 30)
	Digitalis (39 gr)	52	9 sec	6 4 sec	No fainting	5 6 sec

* Symptoms of dizziness more marked than before administration of digitalis

10 *Digitalis*   Detailed observations were made on the effect of carotid sinus stimulation before and after complete digitalization in cases 6, 16, 18 and 26   Table III demonstrates the sensitizing effect of digitalis on the sinus reflex   In cases 18 and 26 more marked reflex slowing of the heart followed digitalization   This sensitizing action of digitalis on the vagal reflex can be seen in figures 6 and 7

In cases 6 and 16, although the tendency to faint was definitely increased by digitalization, there was no increase in the sensitivity of the vagal reflex   Futrhermore, no change in the vasomotor reflex was observed in these two cases   Thus it seems probable that digitalis sensitizes the cerebral as well as the vagal reflex

Case 25 had been completely digitalized before entry and gave a history of attacks of dizziness and fainting commencing after the administration of the drug   The electrocardiogram showed typical digitalis changes   Induced carotid sinus fainting was due to cardiac slowing   The digitalis appeared to play an etiological rôle in this case, although this could not be confirmed because of the patient's early death from pneumonia   We have recently observed 2 additional patients, not listed in this report, who gave a history of severe dizziness and fainting associated with digitalization   In both cases carotid sinus pressure induced fainting due to cardiac standstill and in both cases symptoms were relieved by the omission of the drug

That digitalis can induce stimulation of the vagal center of animals through the induction of increased peripheral stimuli has been shown by Heymans (42), by means of an ingenious cross transfusion technique   He has also shown that an increased sensitivity of the carotid sinus to various stimuli results from the administration of this drug   It seems probable that the same mechanism is effective in man   White (49) mentions that "vagal pressure" produces more marked bradycardia after digitalis has been administered   Koch (50), Heymans (42) and Nathanson (37) (38) have shown in man that digitalis increases the vagal effect on the heart induced by carotid sinus pressure   Our results confirm the above findings and suggest another action of the drug, namely, a sensitization of the cerebral reflex

11 *Sodium cyanide*   It was important in this study to determine whether our patients exhibited an abnormal carotid sinus response, not only to external mechanical pressure but to intrasinal stimulation as well   Sodium cyanide, when administered intravenously, is known to act specifically on the carotid sinus and normally, in adequate dosage, induces transient hyperpnea (42) (35)   In 3 normal persons we have found that the heart rate remains essentially unchanged during the respiratory reaction which follows the administration of a 2 per cent solution of this drug   In patients 24 and 26,

however, in whom mechanical pressure over the sinus induced cardiac slowing, the respiratory response to cyanide was accompanied by definite slowing of the heart rate   In case 24, where fainting was partly the result of a cerebral reflex, symptoms of faintness also occurred   These findings demonstrate that in such patients the carotid sinus is hypersensitive not only to mechanical stimulation, but also to intra-arterial chemical stimulation.

12 *Thyroid extract and dinitrophenol*   Although the very low basal metabolic rates present in patients having the most marked neurotic manifestations were not accompanied by clinical manifestations of thryroid deficiency, it was thought advisable further to eliminate hypothyroidism as a cause for the symptoms by administering thyroid extract   In addition, thyroid extract is known to increase the cardiac output and systemic blood flow (51)   It was given in sufficient amounts to produce toxic symptoms to 2 patients having metabolic rates of minus 25 per cent each   No beneficial effect was noted on either the spontaneous or the induced symptoms, or on other "neurotic" symptoms which were present but not influenced by sinus stimulation

Dinitrophenol, in non-toxic doses, raises the basal metabolic rate to high levels without proportionately altering the heart rate or the cardiac output (52) (53)   When administered to 2 patients of the cerebral type, in doses sufficient to produce metabolic rates of plus 20 per cent, it had no beneficial effect on any symptoms   The initial basal metabolic rates of these 2 patients was minus 25 and minus 13 per cent

Relation of carotid sinus sensitivity to other morbid states

In addition to the sensitizing effect of digitalis on the carotid sinus reflex we have noted a relationship between sinus sensitivity and certain disease states   This has been demonstrated by the diminution of carotid sinus sensitivity coincident with improvement in these conditions

Patient 10 had marked enlargement and tenderness of the cervical glands due to tuberculosis   The patient was having attacks of unconsciousness on an average of three per week and was forced to discontinue school   Pressure over the left sinus produced unconscious-

ness and convulsions within 6 seconds and pressure over the right did so within 20 seconds   The patient received roentgen ray therapy, which resulted in definite local improvement of the glands   During treatment the frequency of attacks decreased so that over a 3 months' period he had only one attack, which followed a blow over the left side of the neck   At the end of this period pressure over the left carotid sinus induced fainting and convulsions within 15 seconds and pressure over the right caused no symptoms   Two weeks later there was an exacerbation of the cervical adenitis   During this period the patient had two spontaneous attacks of syncope and convulsions, fainting was induced by pressure on the right sinus within 8 seconds and on the left within 18 seconds

In patients 11 and 18, who were undernourished, a marked improvement in the induced and spontaneous attacks was noted following dietary treatment   Patient 9, whose attacks were associated with menstruation and emotional upsets, showed marked improvement in both the induced and the spontaneous symptoms between menstrual periods   Patients 20 and 24 also noted a relationship between their attacks and menstruation

Carotid sinus reflex in other unconscious states

As we mentioned previously, we have found the response to carotid sinus stimulation to be normal in many cases of spontaneous syncope of varying etiology   In 3 patients who fainted as a result of postural hypotension, the carotid sinus reflex was normal, while in a fourth case it was abnormal   We have also tested the sinus reaction in 3 patients suffering from narcolepsy   In 1 of these patients the reaction was normal, in the other 2, symptoms of epigastric distress, weakness and faintness were induced, but such symptoms were not present in relation to the spontaneous desire to sleep

Novocainization of the carotid sinus

The tissues of the neck surrounding the sensitive carotid sinus were infiltrated with 1 per cent novocain in cases 1, 2, 3, 4, 5 and 21   In all instances, regardless of the type of syncope and convulsions, every manifestation of carotid sinus stimulation, including fainting, respiratory, pulse and blood pressure changes, was abolished when pressure

was exerted on the anesthetized side   The arterial pressure frequently exhibited moderate temporary elevation following the novocainization, and there was some speeding of the heart rate
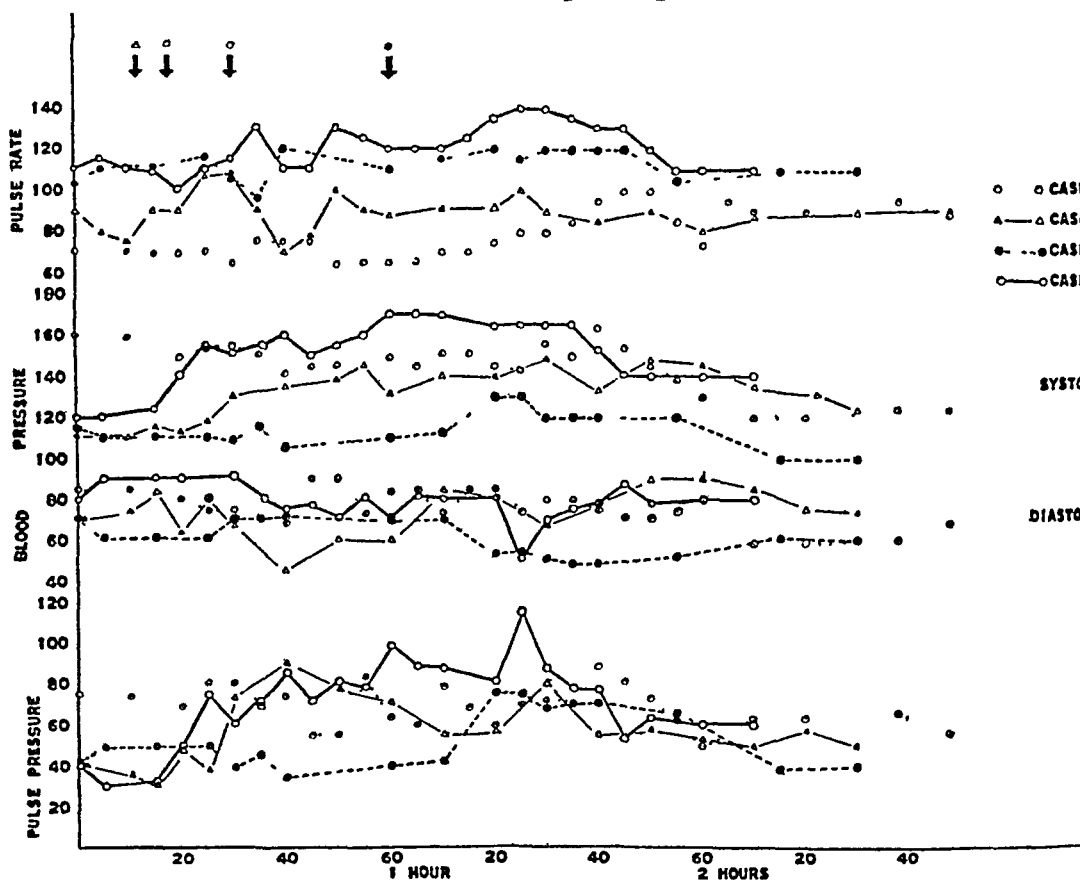

CHART 2   CHANGES IN PULSE, BLOOD PRESSURE AND PULSE PRESSURE IN 4
CASES DURING SURGICAL DENERVATION OF THE CAROTID SINUS

There is a definite rise in the systolic and fall in the diastolic pressure in all instances except case 3   There is also a rise in the pulse rate   All of these changes appear to be transitory   Arrows indicate approximate time of actual denervation

Immediate effect of section of the carotid nerve

A summary of the blood pressure and pulse changes produced by section of the carotid nerve in 4 cases is listed in chart 2   The operations were performed by Dr Donald Munro   The technique consisted in first exposing the carotid artery at the level of the bifurcation   The internal, external and common carotid sheaths were then stripped for a distance of about 2 0 cm above and below the bifurca-

tion   Considerable tissue, consisting chiefly of nerve fibers, was found to be strongly adherent to the carotid sinus superiorly, just at the fork of the bifurcation   This tissue, including the sheaths of the internal and external carotid arteries containing the carotid nerve, was isolated and sectioned about 8 mm above its junction with the carotid sinus   The carotid nerve was not identified at operation, but microscopically the intercarotid tissue removed contained many nerve fibers   In most cases there was a temporary rise in blood pressure and a slight increase in the pulse rate at the time of nerve section No permanent deleterious effect on either the blood pressure or the pulse has been noted in any of these cases

Observations following section of the carotid nerve

All symptoms previously elicited by carotid sinus pressure were entirely abolished, except in case 2, and none of the 7 patients have had spontaneous attacks of either dizziness or fainting since the operation   Case 3 has been observed and followed for 12 months following the operation, cases 1 and 2 for 11 months, cases 4 and 5 for approximately 6 months and cases 20 and 21 for 1 month

The patients have felt greatly improved, both mentally and physically, following the operation, owing largely, we believe, to the fact that they have been able to lead more normal lives   They have been able to return to their usual occupations, a thing which had previously been impossible for them to do   We have been unable to determine any objective difference in the vegetative nervous systems of these patients following operation   The basal metabolic rates, which were usually low before operation, have remained at approximately the same level   In patients 1 and 3 postural fainting was induced before and after operation with the same degree of ease   No change was noted in the skin resistance   The pulse and blood pressure also have remained essentially unchanged   Such manifestations as dermatographia, Raynaud's disease, fatigue, palpitation and angina pectoris, when present, have not been influenced by the operation

In order to determine whether intrasinal reflexes could be induced from the denervated carotid sinus, the reaction to sodium cyanide was tried in case 5, a patient whose right carotid sinus had been denervated   The arm to carotid circulation time was determined by

intravenous injection of 0 25 cc of 2 per cent sodium cyanide, and was found to be 24 seconds (normal about 17 seconds) (35)   Instead of the normal sharp end point, consisting in hyperpnea lasting for 2 or 3 respirations, the hyperpnea began at 24 seconds and continued until 65 seconds, when it was followed by a 10-second period of apnea This reaction is similar to that observed by Robb and Weiss (54) in cardiac decompensation   This same procedure was carried out during occlusion of the left carotid artery (unoperated side) and no reaction whatsoever was obtained   On repeating the test during occlusion of the right carotid artery (operated side) results similar to the control observations were obtained   The result of this experiment was similar on repeated observations   It indicates that the cyanide reaction took place only through the left carotid sinus and that the respiratory response to intra-arterial carotid sinus stimulation was abolished in the right sinus by denervation   This experiment also suggests that the normal respiratory response to cyanide is the result of a summation of impulses from both carotid sinuses

Although every patient was completely relieved of spontaneous attacks and pressure over the denervated carotid sinus induced no symptoms, in cases 1, 2 and 3 we were surprised to find that approximately the same pulse slowing and blood pressure fall occurred after the operations as had occurred before   This is shown in table IV.

Pressure over either carotid sinus failed to produce symptoms in case 2 for as long as 5 months after denervation of the carotid sinus, although about the same fall in blood pressure and slowing of the pulse were present as before   Eight months after the operation, however, marked dizziness and fainting, associated with prolonged asystole, were induced by pressure from both sides, at this time all induced symptoms were relieved by atropin

In cases 1, 3 and 5 pressure on the least sensitive sinus induced symptoms varying in severity from slight dizziness and weakness to actual fainting (case 5)   It is of interest that following carotid sinus denervation the symptoms previously induced from the unoperated sinus were entirely abolished.   The operation had no effect, however, on the changes in heart rate and blood pressure

Since the intercarotid nerve was not identified at the time of operation we are unable to state with certainty that it was sectioned

TABLE IV

Effect of surgical denervation of the carotid sinus

Case number	Initial heart rate per minute	Initial blood pressure	Right carotid sinus stimulation			Left carotid sinus stimulation		
			Heart rate per minute	Blood pressure	Symptoms	Heart rate per minute	Blood pressure	Symptoms
		Before operation						
		mm Hg		*mm Hg*			*mm Hg*	
1	67–73	120/70	37	90/?	Pallor, hyperpnea, dizziness, fainting and convulsions	60	70/?	Slight pallor, hyperpnea and dizziness, mild convulsions, no fainting
2	71–81	156/85	15	90/50	Pallor, dizziness and fainting	38	105/74	Pallor, hyperpnea and slight dizziness, no fainting
3	70–75	120/70	22	85/40	Slight dizziness	63	126/80	Pallor, hyperpnea, dizziness, fainting and convulsions
4	77–100	130/80	120	130/80	Dizziness, fainting and convulsions	77	130/80	No symptoms
5	71–77	126/90	86	132/90	Hyperpnea, dizziness and fainting	86	126/90	Pallor, hyperpnea, dizziness and fainting
		After operation†						
1	68–75	120/80	50	114/76	No symptoms	64	120/80	No symptoms
2*	70–80	155/100–190/110	15	90/?	No symptoms	50	130/60	Slight hyperpnea, no dizziness or fainting
3	75–80	108/66	39	92/44	No symptoms	75–80	110/58	Slight pallor, no dizziness or fainting
4	114	134/74	‡	130/?	No symptoms	‡	128/?	No symptoms
5	72	134/98	72	134/98	No symptoms	72	134/98	No symptoms

* Eight months after operation carotid sinus pressure produced marked asystole and fainting, which were abolished by atropin He has had no spontaneous attacks, however
† The right sinus was denervated in Cases 1, 2, 4 and 5 and the left in Case 3
‡ Very slight slowing

From an anatomical point of view, however, it undoubtedly was, as the first portions of the internal and external and last portion of the common carotid arteries were stripped for a distance of 2 cm above and below the bifurcation, and all the nervous and other tissue adherent to the fork of the bifurcation was severed   Furthermore, at the time of excision of this tissue some increase in the blood pressure and heart rate was noted, suggesting that the nerve was cut (chart 2) The abolition of cyanide response in case 5, as well as the fact that no subsequent spontaneous attacks have occurred in this patient, is strong evidence that reflexes from the carotid sinus itself were abolished   The work of Hering in animals (55) further substantiates such a conclusion   Following denervation of the carotid sinus in rabbits he found that reflexes could still be induced by mechanical stimulation of the sinus but could not be induced by intra-arterial stimulation   Budde (56) has made similar observations in man [5]

DISCUSSION

Relationship of carotid sinus to spontaneous attacks

In the 32 cases studied the spontaneous attacks of fainting appeared to be related to the carotid sinus mechanism for the following reasons (1) Pressure over the sensitive sinus produced symptoms similar to those occurring with spontaneous attacks   (2) Occlusion of the carotid artery below the sinus failed to cause similar symptoms, indicating that simple cerebral ischemia resulting from arterial occlusion

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[5] Since the tabulation of the data included in this paper we have observed the patients who were operated upon for an additional period of 6 months   We have also denervated the sensitive carotid sinus of 3 more patients and have observed them for from 4 to 6 months   During this period the patient referred to as case 1 and one of the 3 patients more recently operated upon have had a recurrence of fainting attacks   The others have remained symptom-free   The symptoms which returned in these 2 patients were not identical with those present before the operation nor could they be reproduced by sinus stimulation, however, the operation can be considered to have been a failure as far as the present state of these 2 patients is concerned   It is of interest that of the entire group of surgically treated patients, these 2 had the severest and most widespread neurotic manifestations   Furthermore, both had basal metabolic rates of minus 25 per cent, whereas the metabolism in the patients that have remained symptom-free ranged from plus 12 to only minus 12 per cent   This suggests that, in patients who have a severe vegetative neurosis as evidenced by widespread symptoms and very low basal metabolic rates, even when the carotid sinus is denervated, syncope of other types may continue   For this reason, such patients may not be proper operative candidates

was not involved   (3) Novocain block of the sensitive sinus abolished all induced reactions   (4) Denervation of the carotid sinus in 7 cases abolished both the induced and spontaneous syncope   (5) In some cases the history suggested that mechanical stimulation of the sinus preceded the attacks   (6) Intravenous sodium cyanide induced mild manifestations similar in nature to the spontaneous symptoms

In view of the neurotic tendencies exhibited by many of the patients it may be contended that these attacks were to some extent "hysterical" in nature   For this reason particular care was taken to prevent suggestion   The fact that control pressure below the carotid sinus, over the eyeballs, in the esophagus and on other points chosen at random failed to precipitate syncope serves as weighty evidence against this possibility   Furthermore, operative cures in 5 cases have so far ranged from 6 to 12 months   Such long periods of recovery are not the rule in hysteria   It is likewise improbable that the bradycardia which occurs in such patients is a hysterical manifestation On the other hand, we do not wish to minimize the fact that many patients with cerebral fainting have exhibited an emotional and sensitive personality and have shown evidence of a certain instability of the vegetative nervous system   The significance of the association of the two conditions will be discussed later

The exact relationship between the carotid sinus reflex and the spontaneous attacks, however, cannot be stated with any degree of certainty   In a few cases, both from our previous report and from the present study, the history clearly indicates a mechanical stimulation of the sinus as the cause of spontaneous syncope   The attacks were induced by changes in position of the head, by pressure from a tight collar, by a blow over the sensitive sinus or by actual pressure due to lying on the sensitive side   Whether in the majority of instances other forms of stimulation of the carotid sinus have played a role, or whether the occurrence of the syncope depended on some abnormal state of the central nervous system which could be brought into action from the carotid sinus reflex, as well as from other afferent pathways, cannot be stated definitely at present

That different types of physiological stimulation of the carotid sinus may result in abnormal reactions in man must be borne in mind Weiss and Baker have suggested that the hypersensitivity of the sinus

reflex depends not only on the hyperirritability of the afferent nerve endings in the sinus, but also on the state of the efferent neurones and of the central synapses   In animals the physiological stimuli include both intrasinal pressure changes and chemical alterations of the blood, as Heymans has shown (42).   We have no definite evidence that such factors play a precipitating rôle in the spontaneous attacks, but the fact that symptoms were induced by release of carotid occlusion below the sinus and by the intravenous administration of sodium cyanide, demonstrates that such mechanisms can occur in man

Heymans' observations with digitalis in animals (42) and our own experience in man have also demonstrated a chemical sensitization of the sinus reflex   Such a chemical or hormonal sensitization may explain the periodic fluctuations of the sinus reflex in certain of our patients

The mechanism of carotid sinus fainting

It has been pointed out before that in this investigation we have concentrated our efforts on a study of the cerebral type of syncope The mechanism of the other two types of syncope related to the carotid sinus has been adequately clarified by Weiss and Baker Although one of the three reflexes plays a dominant rôle in all cases of carotid sinus sensitivity, the other two are usually active to some extent   It is evident that the fainting in the majority of the cases here reported is the result of a direct "cerebral reflex" and has no relationship either to the cardiac slowing or to the fall in blood pressure   In addition to the arguments previously presented, the induction of such symptoms and signs as contralateral numbness, tingling and convulsions of the extremities and ipsolateral numbness of the face suggests a direct cerebral reflex mechanism, particularly since prolonged occlusion of the carotid artery below the sinus failed to induce any such symptoms

It has been suggested by Weiss and Baker that the cerebral type of fainting may be brought about by anoxemia as the result of constriction of the cerebral vessels   In addition to this evidence pointing to reflex cerebral vasoconstriction, we have found changes in the spinal fluid dynamics, associated with pressure over the sensitive sinus and fainting, which strongly suggest that variations in the caliber of the

cerebral vessels frequently occur   It would appear from these data that in most cases, constriction of the cerebral vessels occurs during sinus pressure and that a compensatory vasodilatation occurs on release Although cerebral vasoconstriction appeared before syncope and convulsions, we have evidence that this change in the cerebral vessels is not the actual cause but merely a concomitant manifestation of the fainting   Observations on the effects of histamine and epinephrin in man indicate that the degree of vasomotor changes observed in patients with carotid sinus syncope cannot be held responsible for the symptoms   By observing the pulse oscillations of the brain and of the spinal fluid in man Weiss (57) has found that epinephrin causes cerebral vasoconstriction and that histamine causes vasodilatation   Even when the changes produced by these drugs were more marked than those observed in this study, no symptoms related to syncope were produced

Furthermore, comparative observations on the cerebral blood flow before and during syncope are evidence against the belief that vasoconstriction, if present, is of severe degree or is generalized   The fact that acetyl cholin, amyl nitrite and carbon dioxide failed to influence the attacks is strong but not conclusive evidence against the presence of a localized vasoconstriction, as these drugs may have failed to overcome the reflex vasoconstriction   Thus Weiss and Ellis (58) have observed that cold may induce vasoconstriction in the fingers even during the administration of vasodilator substances such as nitrites and acetyl cholin   Finally, the failure of oxygen to diminish the tendency to faint is against the theory of anoxemia, due to vasoconstriction

The carotid sinus reflex pathways

The fact that in cases 1, 2 and 3 the depressor and vagal responses to carotid sinus pressure remained unaltered or were increased after sinus denervation, while the cerebral reflex was abolished suggests that the pathway of the afferent impulses which produced the fainting was separate and distinct from that which produced the vagal and depressor response   Furthermore, although mechanical pressure on the operated sinus in these cases induced a vagal and depressor response, we have evidence that intracarotid stimulation was without

effect   Thus intravenous cyanide in case 5 failed to produce any response from the operated sinus, and the absence of spontaneous attacks in all operated cases is good evidence that intra-arterial stimuli were ineffective   These findings are difficult to explain because in man the exact afferent pathways of the different reflexes are not known   At operation the intercarotid nerve was not identified although the region of the bifurcation was completely isolated from surrounding tissue, so we are unable to state from our experience whether the sinus nerve alone, the sympathetic and vagal branches to the sinus or still other connections act as reflex pathways. If, as Heymans has suggested, the residual sinus responses are due to direct stimulation of the central stump of the intercarotid nerve it is strange that a cerebral reflex was not also present   Possibly the explanation lies in the existence of a wider distribution of the depressor and cardiac reflex endings than has been previously thought to exist.

We have also found that in a few of the unoperated cases dizziness, faintness and a certain degree of fall of blood pressure and cardiac slowing were elicited when the pressure was applied just below the sinus   The intensity of response, however, was always less than that obtained from pressure applied on the sinus itself   Occlusion of the carotid artery at a considerable distance below the sinus, on the other hand, failed to induce similar responses   At first we assumed that the response obtained in such instances, when pressure was applied below the sinus, was the result of traction on the sinus and hence of indirect stimulation of the intercarotid nerve   This interpretation would be in complete harmony with the observations of Sollmann and Brown (59), who noted bradycardia and fall in the blood pressure upon caudal traction on the central end of the divided carotid artery in animals, a phenomenon depending on stimulation of the sinus nerve, according to Hering   This explanation cannot be offered with any degree of certainty, however, because in some of the patients having a very sensitive carotid sinus, pressure below the sinus was entirely ineffective   A second possibility, therefore, namely that the afferent innervation of the sinus extended over the upper portion of the common carotid artery, cannot be escaped   This suggestion, in the light of our observations, bears some experimental foundation   There are also considerable anatomic and physiological data supporting such contentions

Although the work of Hering and Heymans has tended to attribute
the entire afferent nervous depressor mechanism of the body to the
two pairs of carotid sinus and aortic nerves, there are a number of
observations available which justifiably raise a question against the
validity of such a rigid concept   Braeucker (60) claims, on the basis
of anatomic dissection and histological studies, that both the arch of
the aorta and the carotid sinus receive rich innervation from several
nerves, in addition to the aortic and intercarotid nerves   As far as
the carotid sinus of man is concerned, he claims that it receives in-
nervation not only from the glossopharyngeal nerve, but also from
numerous branches of the vagus, from the superior laryngeal nerve,
from the sympathetic branches of the upper cervical ganglion and a
few branches from the hypoglossal nerve   A comparison of the nerves
originating from the sinus in man indicates that the vagal and sympa-
thetic branches are much more numerous than the innervation from
the glossopharyngeal nerves   One of the most significant findings
made by Braeucker is the observation that although the innervation
of the sinus is the richest, the nerve supply of the bifurcation, as well
as the first portion of the external carotid artery above the bifurca-
tion, is qualitatively identical with that of the sinus proper   A quali-
tatively similar situation was revealed through a study of the inner-
vation of the carotid sinus of rabbits, cats, dogs and monkeys   The
fact that the aortic and the carotid nerves are not the only depressor
nerves is afforded by the claim of Braeucker that isolated section of
the intercarotid and the aortic nerves does not result in permanent
hypertension in rabbits   Only when in addition to the depressor
nerves the entire nervous plexus of the bifurcation, including the first
portions of both the external and internal carotid arteries and the
last portion of the common carotid artery, have been removed did
permanent hypertension ensue   All these observations point to the
fact that the afferent innervation of the carotid sinus in man is not
so sharply localized as was believed, that the innervation probably
shows individual variations and that the afferent impulses can travel
not only through the glossopharyngeal and vagus nerves, but also
through the sympathetic and hypoglossal nerves   Such an interpre-
tation of the innervation of the carotid sinus in man is in accord with
the work of Hatcher and Weiss (61) and Davis, Goode and Weiss

(62), who showed that in animals afferent sympathetic and para-sympathetic impulses from the heart travel both through the sympa-thetic nerves and through the vagi, although the sympathetic nerves carry fewer parasympathetic impulses and the vagus trunk fewer sympathetic impulses

Further evidence that the carotid sinus, as well as the depressor mechanism, is not so sharply localized in man as is believed by Hey-mans and Hering was brought forward by Weiss and Baker (28), who stated that "whether the carotid sinus nerves and the aortic depressor nerves represent a functional entity, so far as an afferent vasode-pressor mechanism is concerned, or whether they are but part of a more extensive afferent vasodepressor mechanism, cannot at present be stated with any degree of certainty   Some clinical and experi-mental observations on arteriovenous fistulas and aneurysms located in various parts of the body strongly suggest the existence of such a widespread afferent vasodepressor system, at least potentially pres-ent in health, and actively present under pathologic conditions Furthermore, the efferent paths of the carotid sinus reflex are often activated not only by the afferent impulses set up within the sinus but also by afferent impulses of other medullary reflexes " The work of Capps and Lewis (18), who induced both depressor and vagal reactions from the pleura in man and animals, further bears this out

Such experimental evidence throws considerable light on the fact that we were able mechanically to induce efferent responses after surgical denervation of the carotid sinus and also by pressing over parts of the carotid artery just outside of the sinus   These observa-tions are not only of theoretical, but also of considerable practical interest, particularly in patients in whom there is a possible relation-ship between the spontaneous attacks and mechanical stimulation of the sinus   In order to obtain optimal results extensive denerva-tion of the sinus and the adjacent carotid arteries should be performed

The observation that atropin and other parasympathetic drugs had no effect on the cerebral or vasomotor reflex shows that these nerve pathways do not behave as parasympathetic structures   Weiss and Baker likewise demonstrated that the depressor mechanism is not affected by atropin, and we have also observed that the respir-atory changes and facial pallor are not affected by the same drug

It was difficult to determine just which part of the reflex arc was abnormal in each patient with carotid sinus syncope   The data obtained by us indicate that a uniform pathology could not be demonstrated in all cases and that the afferent or efferent pathways, as well as the central synapses, may be in an abnormal state, either singly or together   The presence of chronic adenitis and other masses about the sinus, local arteriosclerotic changes, or abnormal dilatation of the carotid sinus suggests involvement of the afferent nerve endings or pathways   The fact that patients with the cerebral type of fainting often lack local pathology but show evidence of an unstable vasomotor system points, on the other hand, to central changes   Finally, in those patients showing marked vagal and depressor sinus reflexes cardiac disease and hypertension have often been present, a fact which points to involvement of the efferent pathway in these types

The sensitizing effect of digitalis on both the cerebral and vagal reflexes is significant   It constitutues definite evidence that this drug acts not only on the vagus but also on other portions of the carotid sinus reflex arc   We cannot state whether the effect on the cerebral reflex is due to a direct or indirect central action or to a direct action on the sinus   The studies of Hatcher and Weiss (63) (64) and the cross perfusion experiments of Heymans (42), however, favor a peripheral action on the sinus itself

We wish, in addition, to point out that the studies here presented demonstrate that in man the afferent impulses originating from the carotid sinus can, through medullary synapses, induce a high degree of alteration in the functioning of the heart, in the peripheral and cerebral vessels, in the respiratory apparatus, in the gastrointestinal canal and in certain parts of the brain   These alterations are often present in different combinations, or they may appear alone   When present in combination they can be separated through the physical and chemical methods herein described

Certain practical considerations

Dizziness is a common complaint in elderly patients and in our opinion is, in many cases, not related to cardiac failure but is due to one of the carotid sinus reflexes or perhaps to other cerebral reflex mechanisms   As patients may develop dizziness and even syncope

during digitalization, it is therefore unwise in the absence of other signs of cardiac failure to administer digitalis to such patients, as it is likely to aggravate the symptoms

The sensitizing effect of digitalis on the carotid sinus reflex also bears pertinently on the problem of preoperative digitalization of elderly patients without congestive heart failure, a procedure often practiced for the purpose of preventing circulatory failure   The development of congestive failure as a result of surgical procedures is a rare occurrence and when it occurs, rapid digitalization can usually adequately take care of the situation after the appearance of symptoms and signs   Preoperative digitalization, on the other hand, increases the excitability of a reflex which may cause not only powerful cardiac inhibition, but also vasomotor depression   The tendency to induce arrhythmias and cardiac standstill is known to be particularly great in patients with coronary and myocardial diseases, the very conditions in which preoperative digitalization is frequently practiced   As a result of either the mechanical procedures indulged in about the neck during the administration of volatile anesthetics, or the increased excitability of the central nervous system during certain stages of the anesthesia, excitation of the carotid sinus during surgical operations must frequently occur   Such factors may well be responsible for some of the sudden cardiac arrhythmias and sudden deaths

The presence of carotid sinus sensitivity has been shown by various observers (28) (65) (39) to be from 50 to 75 per cent in patients with cardiovascular disease   The 32 cases of spontaneous syncope of carotid sinus origin, on the other hand, were found in the course of about 18 months out of a large hospital population, and from a group of patients especially referred to us by physicians   Many more cases of the cardiac type of sinus sensitivity were observed but not studied   Thus, although the three types of syncope are not frequent occurrences, they can no longer be considered mere medical curiosities   The diagnosis depends on the reproduction, promptly and repeatedly, of the spontaneous attacks by pressure over the carotid sinus   Failure to make the diagnosis depends largely upon improper technique in stimulating the carotid sinus and, in our opinion, this fault is largely responsible for the apparent rarity of this condition

The cardiovascular system and syncope of varying etiology

It has been mentioned in the introduction to this report that although syncope is a common clinical manifestation and occurs in a number of physiological and diseased states of the body, its mechanism has been but little understood. Our experience with the three types of syncope induced by stimulation of the carotid sinus demonstrates that the underlying mechanism of even closely related fainting spells can differ. Without a systematic clinical and experimental analysis of syncope occurring in different bodily states it is hazardous to postulate the underlying functional changes responsible for the fainting. As far as the onset of the collapse, the appearance of the patient, the duration of the attack, the relation of the fainting to the orthostatic state of the body and the rapid recovery are concerned, there is a considerable degree of parallelism between syncopes due to various causes. The behavior of the cardiovascular system, on the other hand, reveals considerable variations. In the usual orthostatic syncope that occurs in certain otherwise healthy subjects there is ordinarily a maintenance or even elevation of the diastolic pressure with a slow and progressive decrease of the systolic and pulse pressures, and an elevation of the heart rate, followed at times by a sudden drop, usually simultaneous with the onset of collapse. The blood flow in these cases is diminished (16) (66). In the dizziness and syncope which accompany orthostatic hypotension, there is an abrupt fall in both the systolic and diastolic blood pressures, frequently accompanied by an unaltered cardiac rate. There may be a decrease of the cardiac output. In the syncope which occurs following the ingestion of sodium nitrite there is either a fall in the systolic or in both the systolic and diastolic blood pressures with simultaneous elevation of the heart rate (Weiss and Ellis (40)). Weiss (67) has observed syncope in neuroses in which the systolic blood pressure rose and the diastolic blood pressure fell to zero. This state was associated with intense capillary pulsation in the skin. Syncope of the Adams-Stokes' attack depends primarily on a sudden shift of the cardiac pacemaker and on the resulting asystole or slowing of the cardiac rate. There is always some fall in the systolic and diastolic blood pressure (14). In the syncopes of carotid sinus origin there may be a fall in both the systolic and diastolic blood pressures and

considerable slowing of the cardiac rate, or there may be a fall in both systolic and diastolic blood pressures with maintenance or elevation of the heart rate, and syncope may finally occur without change either in the blood pressure or in the heart rate   In occasional cases other types of blood pressure change may occur, as is shown in figure 3.   Thus various alterations in the cardiovascular system are associated with the same and different types of syncope

The mechanism of transient unconscious states[6]

The occurrence of transient unconsciousness with complete recovery represents one of the interesting and important problems of clinical and investigative medicine   These attacks may be divided into two large groups, best characterized by the terms "faints" and "fits " There are a number of features which are supposed to differentiate the two conditions   Fainting, collapse or syncope is generally believed to depend primarily on changes in the cardiovascular system Such attacks are not preceded by an aura   They occur in the orthostatic state   The collapse is not associated with convulsions or other types of motor manifestations   Recovery of consciousness is prompt and the attacks are not apt to recur   Contrariwise, fits or seizures are believed to depend on primary changes in the brain itself   The attacks are preceded by an aura   They may occur in any position of the body   They manifest themselves in convulsions and other motor functions   The seizures are followed by a period of confusion, and the attacks are apt to return with greater intensity   For practical purposes these differential features have decided merit, and in certain specific types of syncope or seizure they hold true   A cursory examination of the manifestations and of the underlying mechanisms of these two groups, however, fails to support the contention that any of these differential characteristics separate the two conditions   Indeed, practical experience in clinical medicine frequently demonstrates that the classification of certain transient attacks of unconsciousness in one or the other group involves much, and often insurmountable, difficulty   In our experience with nu-

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[6] The term unconsciousness or unconscious state is used in the physiologic rather than the psychiatric sense   It implies sudden loss of contact with the outside world associated with amnesia and loss of voluntary coordinated muscular activity

merous transient states of unconsciousness we have found that cardiac, carotid sinus and other types of syncope may be preceded by an aura They may also be associated with convulsions, micturition, defecation and other involuntary motor and vegetative functions Recovery from syncope, though usually prompt, may be followed by a state of confusion The attacks can recur at varying intervals for a period of years Such types as Adams-Stokes' attacks may develop while the patient is in bed Attacks of "epilepsy," contrariwise, may have all the features of syncope

The significance of the observations presented in this and the preceding study lies in the fact that such clinical manifestations as dizziness, weakness, loss of consciousness and convulsions have been demonstrated to be closely related to each other and could be induced regularly by simply varying the intensity and the duration of stimulus applied over the carotid sinus Furthermore, it is of particular interest that identical manifestations can be induced from the same stimulus and the same site and through possibly identical afferent nervous pathways, but nevertheless through at least three different efferent mechanisms These efferent impulses may manifest themselves in (1) cardiac slowing, (2) primary fall of the blood pressure and (3) cerebral vasomotor changes or some reflex influence on certain parts of the brain It is the latter type of change which has been repeatedly claimed to play a causative rôle in epileptic seizures Thus the carotid sinus syncopes represent ideal examples for the demonstration of all transitions in the mechanisms that underlie characteristic syncopes as well as seizures Furthermore, observations of the cerebral manifestations induced by the stimulation of the carotid sinus give an unusual opportunity to examine the underlying mechanisms of the transient unconscious state and related manifestations

Ever since the first half of the last century when clear cut separation of syncope and seizure had not yet been made, it has been claimed that attacks of unconsciousness depend on cerebral ischemia, the latter being the result of cerebral vascular spasm This concept was first based on the early experimental demonstration of the presence of cerebral vasomotor changes by Claude Bernard, Condres and Brown Sequard (68) and has remained essentially unchallenged up

to the present   As a matter of fact, it received added support from
the more direct demonstration of the nervous control of the cerebral
blood vessels in animals by Forbes and Wolff (69) and others, and by
additional observations in man   Spielmeyer (70) and later Gildea
and Cobb (71) have presented some evidence showing that the lesions
observed in certain patients suffering from epileptic convulsions are
similar to those that can be induced by ischemia and anoxemia   Ken-
nedy (72), Leriche (73) and Foerster and Spielmeyer (74) described
observations on the blood vessels in the exposed human brain just
before the onset of convulsions, which vessels were interpreted as
showing a state of vasoconstriction   Penfield (75), on the basis of
electrical stimulation of the exposed cortex of epileptic patients, has
claimed the presence of a type of vasomotor change in epileptics
which is not present in normal subjects   There was a cessation of
pulsation of the brain during the convulsions

Weiss and Baker (28), on the basis of studies of fainting and con-
vulsions of carotid sinus origin, on the other hand, emphasized that
the simple explanation of ischemia as the cause of convulsions and
fainting is not tenable   They pointed out that even the type of syn-
cope and convulsions which depends primarily on cardiac slowing or
fall of blood pressure cannot be explained on the basis of absolute
degree of ischemia alone   They emphasized that not so much the
absolute degree of ischemia as the rate or the time element of change
from a normal state toward an ischemic state plays a dominant rôle
"Once this temporary but sudden ischemic state develops, a sequence
of events is set up within the brain which then proceed independently
to the development of convulsions, even if a hyperemia promptly
follows the ischemia "   That the theory of generalized cerebral anoxe-
mia is not applicable to epileptic seizures as well has recently been
demonstrated by Gibbs, Lennox and Gibbs (76). By means of a
thermoelectric flow recorder inserted into the internal jugular vein
these authors have obtained evidence which disproves the theory that
acute widespread anoxemia of the brain is an immediate cause of
epileptic seizures

In the light of the observations presented in this study the interpre-
tation offered for the explanation of vagal and depressor types of carotid
sinus syncope does not seem applicable to the explanation of syncope

and convulsions of the cerebral type   Notwithstanding the fact that observations have revealed that just prior to and simultaneously with the onset of the unconscious state there is vasoconstriction of the cerebral vessels, followed by vasodilation, we were unable to demonstrate, either with the aid of blood gas methods or with the electric thermocouple, any appreciable degree of ischemia of the cerebral circulation   Nor did the tendency to faint parallel the degree of cerebral vasoconstriction, as estimated by the degree of facial pallor and change in spinal fluid pulse oscillations   In addition, the fact that syncope could be induced in as short a period of sinus stimulation as 4 seconds or less renders unlikely the possibility of either generalized or localized cerebral ischemia alone playing a primary causative rôle

Thus three closely related interpretations remain for the explanation of such clinical and experimental observations   From our data and from experimental work in the literature, to be described shortly, it appears justifiable to postulate that a special area or areas in the brain for the regulation of the conscious state exist   This "center" must be either (1) especially sensitive to sudden systemic circulatory changes, (2) sensitive to reflex influences, or (3) there must be a localized vasoconstriction in an area so small that it cannot be detected by estimating the total cerebral blood flow   The center or centers may be activated by one or more of these mechanisms   Organic lesions, as far as we know, have not been present in the brains of these patients, a contention adequately supported by the fact that in some cases the response to carotid sinus pressure spontaneously disappeared   In view of this fact, the assumption of any of these possible explanations carries the implication that the unconscious state in the cerebral type of syncope or other types of periodic unconscious states depends not necessarily on changes in the circulation or on reflexes involving the entire brain, but on certain portions of the brain

There exist some experimental and clinical data in the literature supporting the contention that transient unconscious states, such as those which occur in natural deep sleep and in various types of syncopes and seizures, depend on the special function of certain cerebral centers   Experimental studies bearing on the central mechanism of sleep or equivalent unconscious states may be divided into three

types· (a) The concept that regulation of sleep occurs through such chemical agents as the "pituitary sleep hormone" awaits further confirmation   (b) Pavlov (77), using the technique of conditioned reflexes, claims that peripheral reflexes, through their irradiating effect on the cortex, can be responsible for the sudden onset of a sleep-like condition in animals   (c) Spiegel and Inaba (78) have induced "sleep" in animals by producing minute lesions in different parts of the brain with needles   When the needles were inserted into the diencephalon and specifically into the region of the optic thalamus sleep followed, which lasted for weeks, unless the animals were aroused promptly with appropriate stimuli   Certain types of lesions induced transient unconsciousness   Hess (79) has obtained similar results by stimulation of various portions of the brain with needle electrodes Stimulation of the anterior portion of the aqueduct of Sylvius, the inner side of the caudate nucleus and the septum pellucidum resulted in a sleep-like condition   Application of the electrode over other areas failed to induce this reaction   Although Hess could not sharply localize a sleep center, he believes that some function of the para-sympathetic areas is closely related to sleep regulation   In later experiments he (80) induced sleep after injecting minute amounts of ergotamin into certain areas of the third ventricle   Ranson (81) has recently reported work of a similar character   He was able to produce drowsiness and a cataleptic-like state in 48 cats by producing lesions in the lateral hypothalamic areas and in the supramammillary decussation   The oculomotor nucleus was often found to be in-volved   The duration of the drowsiness varied from a few days to weeks   Experiments were also carried out on monkeys and it was possible to cause profound somnolence in these animals as well

Hess enumerates changes occurring during sleep, which indicate parasympathetic inhibition of a number of vegetative functions   He suggests that sleep is a vegetative function controlled by orderly reflexes, the end organs of the reflex being those centers in the brain which serve autonomic functions   The sleep reflex brings about an active inhibition quite comparable to the vagal control of the heart and may be assigned to the same part of the autonomic nervous sys-tem as that to which the vagus is assigned, namely the parasym-pathetic

There are also valuable clinical data bearing on the central regulation of sleep and unconsciousness Economo (82) has correlated the tendency to uncontrollable sleep of patients having epidemic encephalitis with lesions in the midbrain, and places the sleep centers in the diencephalon, where the aqueduct of Sylvius opens into the third ventricle On the basis of the clinical observation that muscular disturbances of the eye often accompany an abnormal desire to sleep, Economo claims that the sleep center must be close to the oculomotor center There are also cases described with circumscribed tumor of the anterior portion of the thalamus and third ventricle in patients with an unconquerable tendency to fall asleep (83) (84)

Hess (80), in a recent discussion of the physiological mechanism of sleep, states "For the time being the question must remain open whether the origin of stimuli is confined to definite parts within the cerebral nervous system, or whether in addition impulses from the periphery are carried to the brain " The work here presented indicates not only that the stimulus inducing sleep-like and deeper unconscious states can lie in the periphery, but that because the pathways of the carotid sinus reflex are fairly well known we can define the mechanisms involved in the reflex

We do not mean to imply from this discussion that the unconscious states we have induced by stimulation of the carotid sinus are necessarily identical with natural sleep or that the accompanying manifestations are necessarily sleep like in nature, as it is obvious that in the majority of instances such is probably not the case However, in a few patients the unconsciousness as well as the other manifestations previously mentioned have closely resembled natural sleep It is of interest that the studies of Hess in animals and our studies on the carotid sinus syncope in man have led independently to similar conclusions Hess has pointed out that sleep is a central inhibition of parasympathetic nature, we have demonstrated a mechanism related to the carotid sinus reflex which can induce, through direct action on the central nervous system, an unconscious state The carotid sinus reflex is considered by Hering to be the most important regulatory mechanism of the tonus of vegetative centers (85) We have demonstrated in man that under a hyperactive state of the carotid sinus reflex a number of well known parasympathetic functions

may become unusually increased   The fact that unconsciousness and convulsions without the presence of generalized cerebral anoxemia can follow such an activity of the carotid sinus points to the concept that certain unconscious states are closely related to the activity of autonomic centers with parasympathetic functions   Judging from the data obtained, we may state that the stimuli that can induce the activity of these centers varies   Sudden vasomotor changes with generalized anoxemia cannot be excluded as one type of stimulus, but apparently direct central stimulation through nervous impulses, through localized vasomotor changes and through certain chemical substances do frequently activate the centers   In this respect the centers involved in the unconscious states behave like some of the other vital centers, such as the respiratory, vomiting and vasomotor centers   These centers can be activated by chemical, and by physical and reflex stimulation

The close correlation observed between unconsciousness and convulsions has been mentioned, although in several of the subjects studied the two conditions have occurred independently   Hence the mechanism underlying the reflex convulsions must be very similar to that of syncope   The teleological explanation offered for the location of the carotid sinus reflex is that it is placed at the point of entrance of the arterial blood column into the brain, a vital organ most sensitive to fluctuations in the circulation, in order to maintain a constant blood supply at an optimal pressure   It is perhaps more than a coincidence that the same mechanism was also found to be closely related to the central regulation of unconsciousness and convulsions   These two functions may also be looked upon as emergency measures for the maintenance of an adequate blood supply to the brain   The occurrence of unconsciousness inhibits many activities leading to fluctuation of the cerebral blood flow, and in addition the change in position of the brain and body from the upright to the horizontal adds a further factor of safety to the cerebral blood supply   Convulsions, on the other hand, are an effective mechanism for improving the blood flow to the brain in the presence of vasomotor failure and may be looked upon as an accessory emergency mechanism in the presence of unconsciousness   Thus the data here presented expand the protective regulatory influence of the carotid sinus mechanism on cerebral func-

tions, although the exact nature of the change in the cerebral centers is not clear   That this protective cerebral function is submerged in health and can become purposeless or even harmful in certain abnormal states of the carotid sinus mechanism is in complete harmony with the behavior of numerous other regulatory mechanisms in human beings

The tonus of the autonomic nervous system and the carotid sinus reflex

In 1910 Eppinger and Hess (86) described the syndromes of vagotonia and sympathicotonia, indicating two conditions which are characterized by the generalized increased activity of the sympathetic or parasympathetic portion of the autonomic nervous system   These syndromes have met with much skepticism mainly because examples of increase in the general tonus of each of the two parts of the autonomic nervous system are seldom, if ever, encountered   Hering (85) in 1932, summarizing the available experimental data on the function of the sinus and aortic nerves in animals, claimed that the afferent impulses of these four nerves play a major role in the regulation of the tonus of the autonomic centers   He contends that the increased activity of these afferent nerves results in an increased tonus of the parasympathetic and a decreased tonus of the sympathetic centers   Koch (87) attaches a purposeful regulatory function to such activity, inasmuch as increased blood pressure, the most important stimulus of these nerves, is usually associated with increased activity and with increased general metabolism   This is then automatically checked and changed toward the normal state through the depressor afferent nerves, which induce an increased activity of parasympathetic centers and a decreased function of sympathetic centers   We have no data which bear on such a generalized influence of the carotid sinus nerves in normal subjects during varied physiological activity   Our studies on patients having abnormal vegetative manifestations suggest, on the contrary, that the carotid sinus is only one of a number of mechanisms which may alter the tonus of the autonomic nervous system   However, the fact that in 4 cases the symptoms induced from the least sensitive sinus were entirely abolished by denervation of the opposite sinus, strongly suggests that tonic impulses from the sensitive sinus had previously maintained

the sensitivity of the centers involved in fainting and convulsions of carotid sinus origin.

In a study of the tonus of the autonomic nervous system in arterial hypertension Patek and Weiss (88) have pointed out that the increased tonus was never generalized but was found only in certain parts of the sympathetic nervous system   The observations presented in this and the previous study (28) offer an explanation for the frequent finding of a localized rather than a generalized increased tonus within a system, or a portion of a system, in disease states As far as the hyperactive state of the carotid sinus reflex is concerned, it has been demonstrated that the effect during stimulation may manifest itself in different organs or portions of an organ in various combinations   Although we have described some factors having a determining rôle in the localization of the motor effects, the complete explanation of these variations is still lacking   In discussing the problem of variations in the motor manifestations of the carotid sinus reflex we have suggested previously (28) that the variations may depend on the behavior of central synapses   "What we consider as the vagal or other medullary center is, therefore, a condensed and busy relay station with some constant, but also with numerous continuously changing activities of sensory and motor connections Some of these active reflexes are innate, some develop with the evolution of the body, others are the result of training, and still others develop with disease " The activity of the carotid sinus reflex in man demonstrates that the function of the autonomic nervous system is under the tonic influence of reflexes, and the knowledge gathered through the study of the sinus reflex offers a rational basis for the explanation of localized changes in the tonus of the vegetative nervous system in other conditions

We have presented evidence that many of these patients who are classified under the cerebral type and some who are classified under the vagal, have exhibited emotional and so-called "neurotic" personalities and abnormal behavior of certain aspects of the vegetative nervous system   They fall into that group of patients vaguely labeled in the past as "vasomotor neurosis," "vasomotor diathesis," "vasomotor instability" or "vegetative imbalance " Just what relationship the sensitive sinus and the vegetative neurosis bear to each

other is not entirely clear However, we attach significance to the demonstration in this group of individuals of a definite and demonstrable physiologic abnormality of the nervous system These patients should be considered as not unlike those with such functional disorders as cardiac arrhythmias or vascular crises Our observations on the abnormal motor responses in these patients suggest that the bodily and psychic reactions of some patients with vegetative neurosis may well depend primarily on an abnormal central and efferent nervous mechanism, rather than on the nature of the psychic experience

SUMMARY

1 This study is based on clinical and experimental observations on 32 patients who suffered from spontaneous attacks of dizziness, weakness and unconsciousness, with or without convulsions, and in whom mechanical stimulation of the carotid sinus promptly induced manifestations of identical nature

2 The clinical and experimental evidence gathered indicates that the spontaneous and the induced attacks depended on hyperactivity of the carotid sinus reflex Patients who did not suffer from spontaneous attacks but in whom attacks could be induced have also been encountered

3 The bearing on the hyperactive state of the reflex of localized lesions of the carotid sinus, certain morbid states of the body, and changes in the function of the autonomic nervous system has been discussed

4 Fluctuations in the activity of the reflex, depending on alterations in certain organic or functional states of the body, have been observed

5 Although the precipitating stimuli of the spontaneous attacks could not be established in all cases reported, instances have been noted in which external mechanical stimulation or changes in the intrasinal pressure were probably responsible

6 The conclusion of a previous study that the hypersensitive state of the carotid sinus reflex depends on the hyperirritability of the afferent, central or efferent portions of the reflex, singly or combined, has been confirmed

7. Unconsciousness, inhibition of function of voluntary muscles, convulsions, changes in the function of cardiovascular, respiratory and gastrointestinal systems were the main efferent manifestations observed

8 Depending on the primary efferent pathway involved, three types of syncope and convulsions have been again described (a) the type depending mainly on inhibition of heart rate, (b) the type depending primarily on a fall in the arterial pressure, (c) the "cerebral type" in which changes in neither the heart rate nor the blood pressure play a rôle

9 The induced attacks of the cerebral type of syncope remained uninfluenced by atropin, pilocarpin, epinephrin, ephedrin, ergotamin, amyl nitrite, acetyl cholin, strychnin, carbon dioxide or oxygen

10 Digitalis has been found to sensitize not only the carotid sinus-vagal reflex, but also the carotid sinus "cerebral" reflex

11 This sensitizing effect of digitalis on the carotid sinus reflex contraindicates its routine preoperative use, particularly in elderly patients

12 Although the cerebral type of fainting was not related to postural hypotension or to experimental orthostatic syncope, it was induced more easily in the upright position

13 The onset of unconsciousness in the cerebral type of syncope occurred as early as 3 to 4 seconds after stimulation, in contrast to the longer time of onset in the cardiac type of syncope

14 Measurements of the cerebral blood flow failed to indicate anoxemia during the state of unconsciousness and convulsions

15 Although cerebral and facial vasomotor changes were associated with attacks in most patients, such changes were interpreted as being concomitant rather than causal manifestations

16 The sensitive carotid sinus has been surgically denervated in 7 cases Complete cure of spontaneous attacks to date has been obtained in every case

17 No permanent change in either the blood pressure or heart rate occurred following unilateral carotid sinus denervation

18 The response to intrasinal stimulation with cyanide was abolished postoperatively. External mechanical pressure still caused changes in the heart rate and arterial pressure although the "cerebral type of syncope" was abolished

19 Evidence is presented that the specific afferent innervation of the carotid sinus in man extends over a greater portion of the carotid arteries and that the communications with other nervous pathways are more extensive than has been heretofore thought

20 Therapeutic denervation of the carotid sinus should include portions of the external, internal and common carotid arteries

21 Symptoms such as dizziness, various types of aurae, muscular inhibitions (cataleptic states), unconsciousness and convulsions are closely related to each other and their induction depends on the degree and duration of the stimulus to the efferent sinus nerves

22 Experimental and clinical findings reported in this study favor a neurogenic mechanism as one cause for fainting, convulsions and other cerebral manifestations

23 The mechanisms and clinical manifestations of syncope (faints) and cerebral convulsions (fits) cannot be rigidly separated

24 The cardiovascular changes that occur in syncopes of varying etiology have been discussed

25 Evidence is available suggesting that localized areas exist in the brain for the regulation of the conscious state   The tonic influence of the carotid sinus on these areas is suggested   The activation of these centers is accomplished through direct reflex action, through localized vasoconstriction or through anoxemia

26 Manifestations of the hyperactive carotid sinus reflex are the result of abnormalities in portions of the autonomic nervous system rather than in the entire system   The mechanism presented suggests that localized clinical manifestations associated with autonomic imbalance depend on hyperactivity of individual reflexes of the autonomic nervous system

CASE REPORTS

No 1, J D This patient, a 42 year old married salesman, complained of fainting attacks for 5 years   At first the attacks came only 2 to 3 times yearly, but during the 6 weeks preceding admission they became much more frequent, occurring as often as once a day   The loss of consciousness followed an aura consisting of dizziness and of numbness over the left ulnar region   Recently this aura also included numbness of the right elbow and of the left corner of the mouth   The loss of consciousness frequently came

on so rapidly that he fell and on several occasions cut his forehead During the syncope, which never lasted more than a few minutes, he had generalized convulsive movements but no loss of sphincter control or biting of the tongue Within a few minutes after the attack he felt perfectly normal except for a transitory headache Although no inciting causes were known, the attacks always occurred while the patient was standing or sitting and never while lying in bed Occasionally, by "exerting his will power," he was able temporarily to postpone or to avert actual syncope

A few months before the onset of the frequent fainting spells the patient was in a motorcycle accident and was knocked unconscious for 4 hours. Shortly afterwards he began to have severe headaches almost weekly, which have continued to the present Occasionally they were hemicranial, and the patient thought they were unrelated to the fainting attacks

For 2 years he had been treated for a duodenal ulcer, found by X-ray, and recently the ulcer symptoms had returned The patient had always been somewhat "nervous," but was especially so during the present illness He was very irritable and wept easily

The rest of the history was irrelevant except that he had had malaria, diphtheria, typhoid, scarlet fever and all of the childhood diseases. He rarely had sore throats and had never had swollen cervical glands

The physical examination was essentially negative except for easily felt and possibly dilated carotid sinuses The blood pressure was 110/80. The results of routine laboratory examination were normal The basal metabolic rate was minus 25 per cent

Pressure on the right carotid sinus produced fainting and convulsions associated with a fall in blood pressure, slowing of the heart rate, facial pallor and hyperpnea The convulsions commenced in the left arm and leg and then became generalized and clonic in type They were preceded by a sensation of numbness and tingling having a similar distribution Pressure on the left sinus produced a slight slowing of the pulse, fall in blood pressure, and a generalized sensation of numbness with mild convulsions, but without syncope Although atropinization abolished the cardiac slowing it had no effect on the symptoms During carotid sinus stimulation the spinal fluid showed changes in pulse oscillations and pressure consistent with constriction of the cerebral vessels There was moderate pallor of the face during carotid sinus pressure with flushing on release The symptoms were not influenced by thyroid extract

The right carotid sinus was surgically denervated on January 11, 1934 Following the operation, stimulation produced no symptoms, although the same degree of fall in blood pressure and slowing of the pulse that occurred

before operation was present   The reaction was unchanged on the left   Nine months after operation no symptoms could be elicited from either sinus although the depressor and vagal effects still remained   He had had no spontaneous attacks during this period

No 2, B F   This patient was a 60 year old married, Jewish shoemaker, who complained of dizzy and fainting spells for 5 months   The dizziness was very frequent and 6 such attacks had culminated in syncope   No precipitating cause was found except that the attacks occurred only while the patient was either sitting or standing   He had an aura of dizziness and so was able to lie down and often prevent actual loss of consciousness   The fainting lasted a minute or two and was not accompanied by convulsions, loss of sphincter control or biting of the tongue   He had developed some palpitation of the heart and dyspnea on exertion during the past year and had also become quite nervous   The family and past histories were irrelevant

The physical examination revealed moderate retinal arteriosclerosis   The carotid sinuses were easily felt and appeared dilated and hard as if calcification were present in the arterial walls   The heart was normal both by examination and by X-ray   The blood pressure was very labile, the systolic varying from 150 to 190 mm Hg and the diastolic from 76 to 110 mm Hg   Laboratory examination was negative except for moderate left ventricular predominance by electrocardiogram   The basal metabolic rate was minus 6 per cent

Pressure on the right carotid sinus induced dizziness and fainting, preceded by numbness of the extremities, and was associated with a fall in systolic blood pressure from 156 to 90 mm Hg and marked slowing of the heart rate   Facial pallor and hyperpnea also occurred   Pressure on the left produced a marked fall in blood pressure but only moderate symptoms   The spinal fluid dynamics showed changes consistent with cerebral vasoconstriction during carotid sinus pressure   During stimulation there was marked pallor of the face, and on release marked flushing, which lasted from 30 to 60 seconds

On January 26, 1934 a surgical denervation of the right carotid sinus was done, and the patient had had no spontaneous attacks of either dizziness or fainting up to 10 months following this procedure   Six months following the operation, pressure over the denervated sinus failed to produce any symptoms (including facial pallor) although the changes in blood pressure and cardiac rate were as marked as before the operation   This indicates that an important cerebral factor was involved in the fainting

An examination 9 months after the operation revealed that the left sinus caused more marked bradycardia and actual fainting on prolonged pressure   Pressure over the denervated sinus likewise resulted in more prolonged asystole than preoperatively and also in fainting   There was some pallor of the face   Atropin abolished the cardiac slowing and the fainting but did not affect the pallor   Spinal fluid changes at this time were similar to those obtained before operation.

No 3, R R   This patient was a 17 year old schoolboy who complained of fainting attacks over a period of 6 months   He had been entirely well up to 1 year before admission, at which time his skin became very oily and he felt nervous and irritable   Six months later acne developed, of sufficient severity to require hospitalization for a period of 2 weeks   Four months before admission he had an attack of weakness described as an "all gone" feeling in the epigastrium.   These symptoms recurred several times until 6 weeks before entry when they became more frequent and culminated in fainting attacks which lasted for 1 to 2 minutes   Since then the frequency of the fainting attacks increased until they occurred every day   The epigastric sensation was a sufficient aura to enable him to lie down when an attack was imminent and so he had never hurt himself   There was no loss of sphincter control   He had occasional mild headaches for several hours after an attack

Recently there was a marked increase in nervousness, irritability and sweating   He began to blush easily and became very constipated   The rest of the history was irrelevant except for swollen cervical glands which accompanied an occasional cold   No history of tuberculous contact could be elicited   For financial reasons the diet had been poor

The physical examination showed a well developed, poorly nourished boy who was quite nervous   The hands and axillae were wet with perspiration and moderately warm   The skin was very oily and there was marked acne vulgaris   A few shotty glands were palpable in the cervical, axillary and inguinal regions   The blood pressure was 110/70   The remainder of the examination was negative   Laboratory studies were entirely normal   The basal metabolic rate was minus 11 per cent

Pressure on the left carotid sinus induced generalized convulsive movements which began on the right, and which were followed by syncope   The early symptoms were dizziness, epigastric weakness, and contralateral numbness of the extremities with ipsolateral numbness of the face   The heart rate decreased slightly and the blood pressure rose about 10 mm Hg   Pressure on the right side caused mild symptoms, but there was definite diminution of heart rate and blood pressure

A surgical denervation of the left carotid sinus was done on December 12, 1933. Three weeks later examination showed that symptoms from right sinus stimulation were slightly but definitely increased, although fainting or convulsions could not be induced. Pressure over the denervated sinus caused no symptoms. The patient has had no spontaneous attacks since operation. The basal metabolic rate has remained unchanged.

Four months later the patient reported that he was working hard, had gained weight and felt better than he had for a long time. He had had no further fainting attacks. Pressure over the right and left sinuses induced no symptoms.

No 4, M II This patient was a 13 year old schoolgirl who complained of fainting attacks of 8 months' duration. The attacks came on suddenly without an aura and nearly always occurred while standing or sitting. Often they were precipitated by sudden turning of her head to the right and very recently she had noticed that she fainted when she touched a certain point on the right side of her neck. The loss of consciousness lasted for only a minute or two and occasionally there were mild convulsions. She never hurt herself or bit her tongue and there was no loss of sphincter control. Upon regaining consciousness there was marked nausea and occasionally vomiting for from 5 to 10 minutes. During the present illness the patient was very nervous and irritable and sweated more than she had previously.

For the past 2 years the patient had frequent colds and sore throats accompanied by tender, slightly swollen anterior cervical glands. For the past 5 years she had weekly attacks of a prickling, blotchy erythema that came and went every few minutes and was often limited to one-half of the body. All her life she had been subject to urticaria after eating certain known foods. The remainder of the history was negative except for intermittent pyelitis since scarlet fever at the age of 6 years. She had had all of the common contagious diseases, including diphtheria. One year before she had had an appendectomy.

The physical examination revealed an obese, apprehensive young girl. The tonsils were cryptic. A few shotty anterior cervical glands could be felt. The heart and lungs were negative. The laboratory examination was negative, including renal function tests. The basal metabolic rate was minus 3 per cent.

Pressure on the right carotid sinus produced fainting in from 3 to 5 seconds, without any change in blood pressure or pulse. Unconsciousness was accompanied by a few clonic movements of the extremities and the

Babinski became positive   Dizziness and hypernea preceded the fainting
On regaining consciousness the patient was nauseated and felt dizzy
Pressure on the left sinus caused no symptoms   Lumbar puncture showed
no changes following sinus pressure not attributable to compression of the
jugular vein and the carotid artery

On May 25, 1934 the right carotid sinus was denervated   Six months
later there had been no recurrence of the fainting, and symptoms could not
be induced by carotid sinus pressure   She felt better than she had for
several years   Four months after the operation she developed chorea and
rheumatic heart disease, which is now quiescent

No 5, E MacK   This 32 year old white, married, Scotch housewife
entered on May 25, 1934 because of fainting attacks for 7 years   At first
the attacks were very infrequent, but during the last 6 months they occurred
as often as every week   The fainting came on suddenly, without aura, and
lasted several minutes   There were no convulsions, no biting of the tongue,
no loss of sphincter control, nor any after effects except momentary amnesia
and mental confusion   The patient had never hurt herself in falling   No
precipitating cause for the attacks was ascertained   They occurred only
in the sitting or standing position

During the last 2 years the patient was more nervous than usual and
was under a severe nervous strain, due to marital difficulties   Four months
before admission she suffered from an attack of amnesia which lasted from
2 to 3 hours   A similar attack occurred just previous to admission and
lasted for 24 hours   She believed that there was no relationship between
this symptom and her fainting

There was no history of sore throats or swollen cervical glands   All her
life she had had marked dermatographia but there was no history of allergy
The family history was negative for epilepsy, insanity and allergic con-
ditions

The routine physical examination was negative except for marked der-
matographia   The neurological examination was likewise negative except
for a fine maintained lateral nystagmus and a questionable increase of the
right knee jerk   Laboratory tests were negative and the basal metabolic
rate was minus 7 per cent

Pressure on either sinus produced fainting without change in the heart
rate or blood pressure   Facial pallor occurred only during left-sided pres-
sure   The fainting was preceded by a sensation of generalized weakness
without the usual sensation of dizziness   The patient stated that just
before becoming unconscious she felt as though she was "going into a natural

sleep " During the recovery period, which lasted for several minutes, the patient, although conscious, was mentally confused and there was profuse lacrimation She later had no recollection of events that occurred during this period

During left sinus pressure, spinal fluid dynamics showed changes in pulse oscillations which suggested cerebral vasomotor constriction

Because repeated tests showed the right sinus to be the more sensitive, this sinus was surgically denervated on June 7, 1934 Shortly following the operation pressure over the denervated right sinus failed to induce any symptoms, while pressure on the left side produced only a slight sensation of weakness

Four months after the operation the patient felt fine, had gained a little weight and said that she was less nervous She had no further fainting attacks, headaches or spells of amnesia The dermatographia was as marked as it had been before the operation Pressure over both the right and left carotid sinus failed to induce any symptoms or changes in the pulse or blood pressure The respiratory reaction to sodium cyanide was absent from the denervated right carotid sinus, but present from the left carotid sinus

No 6, D McN This 46 year old elevator operator entered the hospital because of dizziness and fainting attacks which he had had for from 4 to 5 years The fainting was always preceded by dizziness, which he had learned to relieve by lying down He was an extremely nervous and apprehensive individual The blood pressure was quite variable, it was 190/110 on admission and varied from 150/100 to 130/90 during hospitalization The basal metabolic rate was minus 8 per cent

Both carotid sinuses were sensitive, but fainting was induced only from the left and was accompanied by convulsive twitching of the contralateral arm, and preceded by contralateral numbness and tingling of the extremities There was only slight slowing of the heart rate and fall in blood pressure The spinal fluid dynamics during carotid sinus pressure were suggestive of cerebral vasoconstriction The response to carotid sinus pressure was much more marked following digitalization

No 7, A F This 45 year old laborer complained of dizziness and attacks of fainting for the past 4 years On certain occasions the dizziness was associated with convulsive twitching of the extremities and of the jaw The attacks appeared to come in cycles Following the attacks he was mentally confused for as long as one-half hour He was rather unstable emotionally

The left carotid sinus was the more sensitive and pressure over it duplicated the spontaneous attacks   There was no significant change in the heart rate or blood pressure   He remained confused mentally for several minutes after recovering from the induced syncope   Repeated observations have shown no change in his symptomatology or carotid sinus sensitivity over a 2-year period

No 8, A H   This 40 year old housewife entered complaining of fainting attacks for 6 days   She had previously had occasional attacks of dizziness for 6 years, but during the past 2 months they had increased in frequency until they came daily   During this latter period, financial and other difficulties had caused her to worry a great deal and she had also lost about 10 pounds in weight   The examination revealed multiple dental abscesses and very mild hypertension

On entry, pressure over the left carotid sinus produced pallor, dizziness, numbness and twitching of the contralateral extremities, and syncope   Ten days later, following multiple dental extractions and bed rest, carotid sinus pressure produced the same symptoms and signs to a milder degree but actual fainting could no longer be induced

No 9, J H   A 23 year old housewife entered the hospital complaining of fainting spells of 2 years' duration   Dizziness was very frequent and she fainted at various intervals, usually about once a month   The dizziness and fainting attacks were definitely accentuated by fatigue and emotional upsets   They were also related to menstruation and during 1 day of each period the patient usually had to stay in bed solely because of dizziness   The attacks always occurred when the patient was in the upright position and were relieved by lying down

With the patient in the upright position pressure over the right carotid sinus produced pallor, hyperpnea and fainting, accompanied by contralateral numbness and later convulsions of the arm and leg   In the horizontal position pressure over the right sinus produced dizziness and contralateral numbness, but no fainting or convulsions   No significant slowing of the heart rate or fall in blood pressure occurred

The patient was followed carefully during a period of 1 year and during this time it was noted that the intensity of the sinus reaction varied considerably   In addition to other indefinite factors (psychogenic) it was found that the reaction varied with menstruation   Between periods sinus pressure produced such minor symptoms as dizziness, contralateral numbness and hyperpnea, but no fainting, whereas during menstruation complete unconsciousness could be induced

No 10, E F   A 13 year old schoolboy entered the hospital because he had been having fainting attacks and convulsions over a 3-year period These attacks consisted of unconsciousness and generalized convulsive movements, lasting from 2 to 3 minutes   The patient never bit his tongue and on recovery felt perfectly normal   The attacks were usually associated with fatigue or followed considerable excitement, and recently had increased in number so that he was having from 3 to 4 attacks per week The attacks were usually preceded by an aura of either "weakness in the stomach" or nausea   During childhood he had had an operation on the left side of the neck for tuberculous glands

Physical examination was essentially negative except for numerous slightly tender glands in the left anterior triangle of the neck and a few tender smaller ones in the right   The basal metabolic rate was minus 25 per cent

Pressure over the left carotid sinus for only 6 seconds produced pallor, weakness, fainting and convulsions   A similar but milder reaction was produced by pressure on the right sinus, unconsciousness occurring after 35 seconds of pressure   No change in the pulse rate or blood pressure accompanied these manifestations

Because of the marked glandular involvement, operation was deferred until after X-ray therapy   A definite relationship between the carotid sinus sensitivity, and the degree of glandular inflammatory reaction was noted

No 11, L P   A 45 year old widowed housewife entered the hospital complaining of a sore tongue and diarrhea following a prolonged alcoholic debauch   The diet was inadequate as to meat, fresh vegetables and fruits She had suffered from very frequent dizzy spells for many years, culminating in syncope about once a month   Dizziness usually preceded the fainting and she learned to prevent the latter by lying down   The attacks occurred most frequently during the "hangover" period following her many alcoholic bouts   Examination revealed gastrointestinal and skin lesions typical of pellagra   The patient was also psychotic and very unstable emotionally The cardiovascular system was normal

Pressure over the left carotid sinus with the patient in the horizontal position was followed by dizziness and syncope   There was slight but insignificant change in the heart rate and blood pressure   "Weakness in the stomach" was an early symptom   During recovery from the induced fainting the patient's emotional instability was momentarily accentuated

Three weeks later, after treatment with bed rest, diet and liver extract, the skin and gastrointestinal lesions had healed and the patient was men-

tally clear   At this time the left carotid sinus was definitely less sensitive than it had been on admission   Prolonged pressure with the patient in both the horizontal and upright positions produced pallor, dizziness and epigastric "weakness," but failed to produce syncope

No 12, M C   A 63 year old housewife complained of dizziness for the past year   This dizziness became progressively worse and within the past 5 weeks she had had 5 fainting attacks   These attacks all occurred in the upright position and were relieved by lying down.   There was a history of a diet poor in meat and vitamins and a suspicious history of alcoholism

On physical examination she was found to have an enlarged heart, a blood pressure of 200/105 and evidence of marked generalized arterio-sclerosis

Pressure over either carotid sinus induced marked pallor, dizziness and syncope   There was a moderate fall in blood pressure, independent of the cardiac slowing, which was insufficient in magnitude to cause fainting

No 13, J C   A 59 year old laborer entered the hospital because of attacks of epigastric pain 2 to 3 hours after meals over a period of from 3 to 4 years   A duodenal ulcer had been found by X-ray 2 years before He had been severely constipated for 30 years   He also complained of occasional fainting and dizzy spells over a period of years   The uncon-sciousness was always of short duration and he never hurt himself during the attacks   They occurred only in the upright position   The physical examination was essentially negative   He appeared to be emotionally unstable

Pressure on the right sinus induced generalized convulsions and fainting without significant change in the heart rate or blood pressure   Pressure on the left caused nausea and retching with dizziness and convulsions but without fainting

No 14, E Q   This 24 year old male had been having attacks of dizziness and fainting sporadically for the past 14 years   They had become more frequent during the past 6 months   The fainting was preceded by an aura of epigastric "weakness," generalized weakness, and dizziness   The attacks occurred only in the upright position and were relieved by lying down   The patient was emotionally unstable and mentally subnormal   The physical and laboratory examinations were negative   The basal metabolic rate was minus 17 per cent

Although both sinuses were sensitive, actual fainting could be produced

only by pressure on the right sinus while the patient was in the upright position   Syncope was accompanied by facial pallor, slowing of the heart rate and fall in blood pressure, marked generalized convulsions and internal strabismus of the left eye   Atropin prevented fainting and abolished the changes in heart rate and blood pressure, but mild convulsions and facial pallor could still be induced   It was concluded that the symptoms were due partly to the cardiac slowing, and partly to a direct cerebral reflex

No 15, J L   This 61 year old machinist entered the hospital primarily because of a subdeltoid bursitis   For several years he had been troubled with frequent dizzy spells, and within the past year had fainted on 5 occasions   The fainting was always preceded by dizziness, and he learned that sitting or lying down, if accomplished in time, would prevent fainting

Clinical studies revealed that the patient had active central nervous system syphilis   The blood pressure was very unstable, ranging from 150/70 to 104/60

Both carotid sinuses were found to be sensitive, but actual fainting could only be produced by pressure on the right   Marked pallor and hyperpnea, and convulsions of the contralateral extremities preceded the actual fainting   There was likewise a moderate degree of fall in blood pressure and slowing of the heart rate   The spinal fluid dynamics during pressure showed the characteristic cerebral response

No 16, A D   This 63 year old spinster entered the hospital because of tingling and numbness of the extremities of 2 years' duration and attacks of dizziness for the past year   During the last 3 months the dizziness had become more severe and on many occasions she had felt as though she would have fainted had she not assumed the horizontal position   Actual fainting occurred only once

The blood and spinal fluid Wassermann were positive and there was evidence of early tabes dorsalis   Pressure on the left carotid sinus produced pallor, mild twitching of the contralateral extremities and syncope, associated with a moderate fall in blood pressure   She had subjective symptoms of dizziness, weakness and numbness of the contralateral extremities when either sinus was stimulated   Observation of the spinal fluid dynamics during left carotid sinus pressure showed the "cerebral" reaction   Ergotamin had no appreciable effect on the reaction but the moderate fall in blood pressure obtained previously was abolished   Digitalis was found to sensitize the fainting reaction although no cardiac slowing occurred

No 17, R S   A 71 year old man entered the hospital complaining of choking and fainting attacks which he had been having over a period of 10 weeks   The choking was associated with cough, came at any time of the day or night, and was not related to exertion   During this period he had had very frequent attacks of dizziness associated with a sensation of smothering, these attacks occurred when the patient was in a standing position He had fainted on 3 occasions

Physical examination revealed a generalized glandular enlargement, particularly in both anterior triangles of the neck, and also a palpable spleen   The cardiovascular system was normal for an individual of the patient's age   The electrocardiogram was negative except for changes in rhythm consisting of marked sinus arrhythmia and many premature ventricular beats   Biopsy of a gland demonstrated lymphosarcoma

Pressure on both the right and left carotid sinus produced symptoms similar to the spontaneous ones, consisting of marked dizziness, faintness, hyperpnea and cough   There was no change in the heart rate and there was a fall in the blood pressure of only 20 to 30 mm Hg

No 18, F F   A 46 year old longshoreman entered the hospital complaining of weakness of 4 years' duration   During this time there had been frequent attacks of dizziness and during the past 2 years this had culminated in fainting on 6 or 8 occasions   There was a long history of peptic ulcer associated with inadequate diet   He had had glands removed from both sides of his neck 30 years before   He stated that he had always been rather nervous and irritable

At the time of the physical examination the patient was pale and undernourished   He was extremely restless and irritable   The liver was palpable   The heart was negative and the blood pressure 130/76   The laboratory examination revealed a moderate hypochromic anemia and a positive Takata-Ara reaction which suggested cirrhosis of the liver.

Pressure over the left carotid sinus caused pallor, dizziness, convulsions and syncope, accompanied by marked but very temporary slowing of the heart rate   Pressure over the right carotid sinus produced no symptoms After the patient was digitalized the reaction from the left sinus could be produced much more rapidly than before and pressure over the previously insensitive right sinus also induced fainting and convulsions   Following digitalization the fainting was accompanied by prolonged cardiac asystole

Two months later, after treatment with a high-vitamin diet, liver extract and iron, the patient had had no spontaneous attacks of either dizziness or fainting   Pressure over the left sinus produced some pallor and mild con-

vulsive twitching without unconsciousness   Pressure over the right sinus had no effect

No 19, L B   A 43 year old tailor complained that over a period of 7 months he had had attacks of dizziness severe enough to prevent him from working   The symptoms always occurred while the patient was sitting or standing and were relieved by lying down   The blood pressure was very variable and fluctuated from 180/100 to as low as 126/80 on different occasions   A diagnosis of mild hypertension and hypertensive heart disease was made

Both carotid sinuses were found to be sensitive but syncope could be produced only from the left   Pressure on either sinus induced symptoms of dizziness, blurring of vision, and contralateral, followed by generalized convulsions   The greatest fall in blood pressure and slowing of the heart were induced from the right sinus

No 20, C D   This 36 year old female was referred to us because of frequent attacks of dizziness and fainting   The history of dizziness extended over a period of 4 years and she had fainted 5 times within the past year   She noted that dizziness was brought on by any movement of the head which put traction on the left carotid artery, and it also occurred when she wore coat collars which pressed against the left side of her neck   The attacks were worse during menstruation   Many spells occurred for no ascertainable reason

The patient had known for many years that she suffered from congenital dextroposition of the aorta, which had produced symptoms of esophageal obstruction and irritation   She also had frequent attacks of severe pain which radiated up the left carotid artery and localized at the angle of the jaw   This pain was often initiated by eating and also by positions of the head that placed traction on the left carotid artery   Both this pain and the dizziness were partially relieved by a position in which the head was held down and the shoulders slumped forward

During childhood, tuberculous glands had been removed from the left side of the neck

The physical examination revealed that the left common carotid artery pulsated more forcefully than the right   A few small glands were palpated in the left anterior triangle of the neck   The aortic second sound was loud and snapping and was transmitted down the right side of the sternum   The blood pressure was very variable, ranging from 120 to 152 mm Hg systolic and from 80 to 90 mm Hg diastolic   X-ray and fluoroscopic

studies revealed a right-sided aorta which crossed the midline posterior to the esophagus   The esophagus was markedly constricted at this point and dilated above

Pressure on the left carotid sinus induced marked dizziness, weakness of the extremities and faintness, without actual unconsciousness   These symptoms were associated with a slight fall in the systolic and a slight rise in the diastolic blood pressure without change in the heart rate   There was moderate hyperpnea   Traction on the left carotid artery induced by forcing the head back and to the right caused similar manifestations but to a milder degree   Occlusion of the carotid artery below the sinus was without effect, but on release symptoms of dizziness and weakness occurred momentarily

Epinephrin, ephedrin and atropin were found to have no effect on either the spontaneous or the induced symptoms

The patient insisted on operative interference and the left carotid sinus was surgically denervated on December 11, 1934   A few small glands were found in the region of the carotid bifurcation but no other abnormality was noted   Three weeks following the operation there had been no recurrence of symptoms

No 21, S G[7]   A 62 year old married Greek merchant entered because of attacks of faintness and of numbness of the hands and feet of from 6 to 8 years' duration   These spells occurred only when the patient was in the erect position and were often precipitated by exertion or extending the head while turning to the left.   The numbness was usually of the left arm and leg and the right side of the face and was accompanied by an "all gone" sensation   The attacks lasted only a few minutes and were relieved by lying down   There had been no complete loss of consciousness, but the patient felt that he was incapacitated   He also complained of occasional right hemicranial headaches and heartburn   He had been a very nervous and highstrung individual   There was no history of sore throats or swollen cervical glands

The examination revealed no abnormalities   X-ray of the gastrointestinal tract demonstrated a duodenal ulcer   No obvious arteriosclerosis was present   The basal metabolic rate was plus 14 per cent

Pressure on either side produced contralateral numbness followed by convulsions of the extremities and ipsilateral numbness of the face   Fainting ensued after about 10 seconds of pressure on the right and about 20

[7] This case was a patient of Dr J C White of the Massachusetts General Hospital, who has kindly allowed us to include him in our group   He was observed by one of us

seconds on the left   Although the right sinus was the more sensitive, there was very little change in the blood pressure or pulse on this side, indicating a cerebral type of reaction   Novocainization abolished the reflex   It was also of interest in this case that occlusion of the carotid artery low in the neck produced no symptoms except on release, when there was a marked reaction similar to sinus pressure on that side

On November 27, 1934 the right sinus was denervated by Dr J C White

No 22, A R   A 57 year old housewife was referred to the hospital because of dizziness, fainting and shortness of breath

She was known to have had pulmonary tuberculosis for 25 years as well as tuberculous cervical adenitis in childhood   For a number of years she had been troubled with some shortness of breath on exertion and had always had a slightly productive cough   She had always been extremely nervous Attacks of dizziness and weakness and occasional fainting had been frequent for 20 years   During the past year the attacks had become more severe, and in association with these attacks she had become markedly short of breath, which symptom became a part of the syncope attacks These symptoms, including the dyspnea, were brought on particularly by excitement or worry and also by extending the head upward   They were relieved by lying down

The physical examination revealed the presence of small glands on both sides of the neck   There was lordosis of the cervical spine   The carotid arteries appeared dilated and tortuous   There were signs of emphysema and of bilateral tuberculosis with cavitation and fibrosis on the right   The heart was normal in size and the blood pressure 190/100   There was marked clubbing of the fingers

Fainting was induced from both carotid sinuses, the left being more sensitive   Stimulation of both sinuses induced slight changes in the heart rate and blood pressure   Stimulation of either sinus induced marked pallor, and symptoms of dizziness, marked weakness, fainting, lacrimation and marked hyperpnea, the latter symptom lasting from 1 to 2 minutes after the return of consciousness   Extending the head upward and backward induced similar manifestations   Actual fainting could be induced only in the upright position

No 23, M K   This 42 year old housewife entered the hospital following a fainting spell   Since childhood she had suffered with transient periodic attacks of fatigue and weakness, during which she yawned frequently and

felt a desire to sleep   Three months before entry these attacks had become more frequent and were associated with generalized weakness, and numbness and tingling of the hands   These symptoms were brought on more easily by overwork or loss of sleep, always occurred in the upright position and were relieved by lying down   Within the past month she had "fainted" on three occasions and had injured herself each time   The fainting consisted of complete collapse due apparently to sudden motor weakness, without actual loss of consciousness   During these attacks vision was blurred, she felt sleepy and was unable to move the extremities   She recovered within a minute and remembered all events that occurred during the episodes   The physical examination revealed a small gland just over the left carotid bifurcation   The blood pressure was 170/100   The patient was emotionally unstable   Laboratory examination revealed a red blood count of 6 37 million per cu mm and a hemoglobin of 66 per cent

Pressure on the right sinus induced moderate symptoms of weakness, blurring of vision, and numbness and tingling of the hands   In addition to the above symptoms, pressure on the left sinus induced complete motor collapse   The patient became limp, closed her eyes, and was unable to support herself or to move, although she was still conscious of her surroundings   She described these symptoms as being identical with the spontaneous ones, including the sensation of falling asleep   There was no change in either the pulse or blood pressure   Respirations became slightly deeper   Both the spontaneous and induced symptoms were identical with those encountered in patients suffering from catalepsy

No 24, S M   This 46 year old housewife complained of attacks of dizziness and fainting which had begun 2 years previously   At the onset she had had attacks of weakness and dizziness which occurred only during her menstrual periods   These symptoms had gradually increased in severity and had become more frequent until 1 year before entry when actual fainting had occurred during menstruation   The fainting attacks then began to increase in frequency until at the time of entry the patient was fainting every day and was feeling continuously weak when in the upright position   Fainting was also preceded by pricking sensations in the fingers, epigastric distress, nausea and the sensation of "going to sleep "   Although the attacks were relieved by lying down they usually came on too rapidly to be prevented by such a measure   The unconsciousness lasted for only a short period and the patient felt perfectly well after recovery, except for nausea on occasions   She had been subjected to a subtotal thyroidectomy 5 years before and had since noted a gradual enlargement of her neck   The

physical examination revealed that both lobes of the thyroid were enlarged A large non-tender lymph node was palpable at the angle of the left mandible   The cardiovascular system was normal   The skin was pale   The laboratory examination revealed a red blood count of 4 1 million and a hemoglobin of 60 per cent   The basal metabolic rate was plus 4 per cent

Pressure over the right carotid sinus was without significant effect Pressure over the left sinus induced symptoms identical in nature to the spontaneous attacks   These were dizziness and marked generalized weakness, tingling of the contralateral hand followed by generalized numbness and tingling, epigastric weakness, unconsciousness and convulsions   Pallor of the face and moderate slowing of the heart rate occurred   After recovery the patient became nauseated and vomited   Intravenous sodium cyanide induced symptoms of weakness, faintness and nausea when given in sufficient amount to induce a respiratory reaction

No 25, P McC   A 38 year old police officer entered the hospital because of a fainting attack which had occurred during an alcoholic debauch   He had been a steady drinker for the past 5 years and there was a history of marked dietary deficiency   During the past 2 years he had suffered from frequent dizzy spells which culminated in unconsciousness on several occasions   A physician had recently prescribed digitalis   At the time of the examination the patient obviously had delirium tremens with visual and auditory hallucinations   There was evidence of marked malnutrition in that the patient had characteristic signs of pellagra as well as moderately severe hypochromic anemia   An electrocardiogram showed T wave changes characteristic of digitalis intoxication

Pressure on either carotid sinus induced convulsions with unconsciousness from the left, and disorientation without definite loss of consciousness from the right   Prolonged cardiac asystole and marked fall in blood pressure also occurred   Atropin abolished all symptoms as well as the changes in heart rate and blood pressure

It was of interest in this case that on recovering from the induced state of unconsciousness the patient was mentally confused and disoriented for several minutes, during which time he had visual and auditory hallucinations and loss of memory   These manifestations could be induced after he had become mentally clear under ordinary conditions   The fainting was due purely to cardiac asystole

No 26, D K   A 66 year old Jewish male entered because of a fistula in ano of 3 months' duration   For 2 years he had also had occasional spells

of dizziness   These always occurred in the upright position, lasted several
minutes and on one occasion culminated in unconsciousness   For the last
year he had also noted dyspnea on exertion and occasional attacks of pre-
cordial pain   On examination, the fistula in ano was noted and in addition
he was found to have polycythemia vera with a red blood count of 8 0
million   The blood pressure was 190/110 and there was evidence of bron-
chiectasis at the right lung base   Following operative treatment of the
fistula the blood pressure fell to a level of 130/80 and thereafter showed
marked fluctuations

Pressure on either carotid sinus produced hyperpnea, pallor and dizziness,
but fainting and convulsions occurred only from the right   This was
associated with a marked decrease in the heart rate   Atropin abolished
syncope and asystole but hyperpnea, pallor and dizziness could still be
elicited   It was also possible to show, by means of a continuous blood
pressure tracing, that stretching the neck by forcing the head back and to
the left produced a definite diminution in the heart rate and blood pressure

No 27, A R   A 54 year old housewife entered the hospital with a chief
complaint of arthritis of 4 years' duration   She had had frequent fainting
attacks during childhood   Over the past 5 years she had had numerous
attacks of severe dizziness and was forced to lie down to get relief   The
physical examination revealed evidence of advanced atrophic arthritis
The blood pressure was very unstable, ranging from 180/96 to 110/70

Pressure on the left carotid sinus produced a moderate fall in blood pres-
sure without causing any subjective symptoms   Pressure on the right
caused dizziness and fainting   There was marked sinus bradycardia, with
asystole ranging from 2 1 to 6 4 seconds   The symptoms of dizziness and
fainting, however, did not vary proportionately

No 28, L L   A 55 year old negro male entered the hospital complaining
of a recent epistaxis and dizziness   He was known to have had hyper-
tension, tabes dorsalis and pyelonephritis for a number of years   Evidence
of marked arteriosclerosis and of mild Parkinson's disease was also found
The blood pressure was 186/120 and the electrocardiogram showed left
ventricular predominance and T wave changes suggestive of coronary
disease

Pressure on either the right or left carotid sinus induced fainting and
convulsions, accompanied by pallor of the face and labored respirations
Simultaneous electrocardiographic tracings showed complete asystole, due
to S-A block, during the entire duration of pressure   Atropin abolished the
asystole as well as the fainting and convulsions   Sinus pressure, however,

still produced some mental confusion and a considerable fall in blood pressure, and the respiratory changes and facial pallor were likewise still present On several occasions Parkinsonian movements of the hand, although not present beforehand, were brought on by sinus pressure

No 29, C M   A 56 year old male food packer complained of severe dizzy spells which he had been having for 1 year   The dizziness occurred regularly on arising in the morning and always when the patient was in the upright position   It was relieved by lying down

The physical examination revealed moderate emphysema, the heart was negative   The electrocardiogram revealed frequent dropped beats due to sinoauricular block

Pressure on either the right or left carotid sinus produced a feeling of marked dizziness similar to the spontaneous attacks   More prolonged pressure on either side produced unconsciousness and convulsions, accompanied by prolonged cardiac asystole due to sinus block

No 30, M L   This 44 year old housewife had been suffering with abdominal crises and shooting pains for the past 12 years as a result of tabes dorsalis   Over the last 7 years she had had very frequent attacks of dizziness and occasional fainting   The attacks had occurred most often in the mornings when she arose from bed and assumed the upright position   However, many attacks had occurred at other times   She would lie down when she felt an attack coming on and thus was often able to prevent actual unconsciousness

The physical examination revealed the typical signs of tabes dorsalis There was mild postural hypotension   The blood and spinal fluid serology were positive   The basal metabolic rate was minus 3 per cent

Pressure on the right carotid sinus produced pallor, hyperpnea, marked dizziness and contralateral convulsions   The heart rate did not change significantly but the blood pressure fell from 154/84 to 90/60

No 31, J W   This patient was a 48 year old male baker who complained of attacks of dizziness of short duration which he had had for 2 weeks Thirty years previously he had suffered a sunstroke and since then had been very nervous, had had palpitation and had sweated a great deal   Four years before admission he had developed ulcer symptoms and a duodenal ulcer had been found by X-ray   These symptoms had recurred intermittently The physical examination was essentially negative   An electrocardiogram was suggestive of acute coronary thrombosis

Pressure on either carotid sinus produced marked pallor, dizziness and generalized convulsions, but actual fainting occurred only from the right It was accompanied by a moderate decrease in the heart rate and blood pressure

No 32, G E   A 57 year old male entered the hospital out-patient department complaining of dizziness and attacks of fainting which he had been having for 2 years   The attacks usually occurred in the upright position, although he also complained of similar attacks of dizziness which were accompanied by a smothering sensation and which occurred while he was lying in bed   These latter attacks were brought on only when he assumed a position which caused pressure on the left side of the neck   The physical examination was essentially negative except that the patient appeared to be emotionally unstable   The blood pressure was 130/80 and there was no evidence of heart disease

Pressure over the left carotid sinus produced dizziness and fainting similar to the spontaneous attacks and was accompanied by moderate slowing of the heart and fall in blood pressure   It was thought probable that the nocturnal attacks were related to the fact that pressure was being exerted over the sensitive left sinus   The response to right sinus stimulation was normal.

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INTRAPLEURAL PRESSURE IN HEALTH AND DISEASE AND ITS INFLUENCE ON BODY FUNCTION

MYRON PRINZMETAL[1] AND WILLIAM B KOUNTZ

From the Department of Internal Medicine, Washington University School of Medicine and Barnes Hospital, St Louis, Missouri and the Departments of Pharmacology and Thoracic Surgery, University of California Medical School, San Francisco, California

A INTRODUCTION

The intrapleural pressure, or the pressure in the potential pleural cavity, results from the counterplay of two forces   The lungs, which normally fill the pleural space completely, contain a large amount of elastic tissue which constantly tends to pull them away from the chest wall   On the other hand, since the pleural cavity contains no air and the two pleural surfaces are slightly moistened by pleural fluid, there is a strong cohesive force which tends to keep the lungs in apposition with the thoracic wall   The result is a negative or subatmospheric pressure in the intrapleural space   When the chest expands in inspiration, there is a tendency to pull the chest wall away from the lungs, and the counterforce exerted by the pulmonary elastic tissue becomes still greater, so that the intrapleural pressure becomes *more negative*   When, however, the muscles of inspiration cease contraction, as they do at the end of inspiration, the chest cavity decreases in size and relatively little pull is exerted on the elastic tissue of the lung, hence the intrapleural pressure becomes *less negative* and approaches more nearly that of the atmosphere

B HISTORY

In the early Greek writings references are found which indirectly refer to the intrapleural pressure   It seems that a common method of executing criminals was by means of an open pneumothorax   That physicians also recognized the importance of the intrapleural pressure

is indicated by the writing of Celsus (29) who states that "as soon as the knife reaches the thorax and cuts the transverse septum (called the diaphragm), the man at once gives up the ghost and thus it is the breast and viscera of a dead and not a living man which the murderous physician examines"

Vesalius (117) was the first in modern times to note the effect of opening the chest in a living animal   After a careful dissection of the ribs and intercostal muscles he noted,

a great stretch of costal pleura, which, being transparent displays the motion of the lungs   This membrane being broken one may see the lungs fall away from the side wall and the lungs are seen as a result of the perforation to fall together and collapse   The cardiac motion may not be observed for long, since suffocation of the animal will come, on account of the collapse of the lungs

In order to restore the life of the animal an opening may be made in the upper part of the trachea in which a pipe made from reed is introduced When the reed is blown into, as the lung rises up, the animal receives air. The heart now gathers new strength and the motion will change beautifully Thereafter, by maintaining repeated inflation of the lungs, you may have an opportunity to examine the motion of the heart both by touch and sight.

Carson (27) in 1820 by an ingenious experiment and deduction greatly added to our knowledge of the rôle played by pulmonary elasticity in respiration and circulation   By means of an intratracheal cannula connected to a water manometer, he studied variations on intratracheal pressure in different animals   When the chest was opened he noted that the intratracheal pressure became greater as the lungs collapsed   He pointed out that the lungs collapsed because they were elastic and that this elasticity played an important rôle in respiration and circulation   He was even far-sighted enough to realize that the elasticity might be a hindrance to healing of many pulmonary diseases and urged pneumothorax as a therapeutic method in the treatment of pulmonary tuberculosis and other conditions   He also emphasized the importance of collapse in the treatment of hemoptysis   He states, "The sides of the abscess are prevented from falling into contact not by the matter which lodges between them but by the powerful elasticity and retraction of the surrounding substance"

Under Carson's supervision pneumothorax was attempted on two patients with far advanced pulmonary tuberculosis Unfortunately, extensive adhesions prevented the collapse of the lungs and this procedure was not utilized for the next 65 years

Carson's experiment was repeated many times both in normal and in pathological lungs   Donders (47), using Carson's method, observed that when the lungs were inflated to their inspiratory position, the intratracheal pressure was greater than with the lungs in their expiratory position   For this observation Donders has received so much credit that the intrapleural pressure has been frequently referred to as "Donderische Druck," an honor perhaps not entirely justified in view of Carson's earlier observations   Although observations on dead animals are of considerable theoretical importance, their applicability to the study of function in living animals has been questioned, chiefly because changes in pulmonary elasticity occur soon after death

Potain (105a) in 1848 treated a case of spontaneous hydropneumothorax due to tuberculosis by replacing fluid with sterilized air   He measured the intrapleural pressure in this case   Because of the good therapeutic result, he advocated the use of pneumothorax for the treatment of pulmonary tuberculosis and advised that the intrapleural pressure be maintained between 7 mm of mercury and atmospheric pressure

The first successful determination of intrapleural pressure in normal living man was made by Aron (4) in 1891   In 36 determinations on one subject, he found the average tension at the end of quiet inspiration to be $-4\ 6$ mm of mercury and at the end of expiration $-3\ 02$ mm of mercury   He also observed that the pressure was more negative in the upright than in the recumbent position   He demonstrated that in both open and closed pneumothorax in the rabbit there was a rise in the intrapleural pressure on the affected and also on the opposite side

In 1880 Lucioni and Rosenthal (87) showed in experimental animals that the mediastinal pressure was also subatmospheric, an observation which was repeated in man by Rosenthal and Leube (108)

A more detailed survey of the earlier investigations on intrapleural pressure appears in a review by Heynsius (73)   Recent work on the subject has been more concerned with open pneumothorax because of

its importance in thoracic surgery   A complete review of this phase of the subject appears in a monograph by Graham (63)

C. NORMAL VARIATIONS OF INTRAPLEURAL PRESSURE

I Definition

Wirz (126), and more recently Christie (32), have classified intrapleural pressure as *static* when the lungs are at rest and *dynamic* when measurements are made during inspiration or expiration   Since the dynamic intrapleural pressure varies directly with the amount of air respired, it will change greatly between the limits of the most shallow respiration and the vital capacity   The extreme positive and negative pressures which occur with forced expiration or inspiration can only be obtained by taking the intrapleural pressure during the Valsalva or the Mueller experiments   During the former, which consists in exerting the maximum expiratory effort against a closed glottis, as occurs in coughing, the intrapleural pressure is greatly increased and may reach a positive pressure of 60 cm of water (49, 83)   Conversely in the Mueller experiment, which consists of a maximum inspiratory effort against a closed glottis, the maximum negative pressure may be attained   Under such circumstances the intrapleural pressure may drop as low as −50 to −60 cm of water (49)   Maximum variations in the intrapleural pressure are probably of more significance than variations in the intrapleural pressure taken during ordinary breathing. They are, however, far more difficult to ascertain

II Method of measurement

Since the pleural cavity in the normal individual is only a potential space, it is impossible to record pressure unless there is at least a small pneumothorax pocket   Usually the introduction of a small amount of air occurs when the needle reaches the pleural cavity due to the negative pressure which sucks air into the chest   For recording changes of pressure during tidal air movements a small pneumothorax may be sufficient   From 30 to 50 cc of air may be used in man without modifying appreciably the intrapleural pressure readings (33)

Intrapleural pressure readings should be made with a large trocar or needle, since a large bore offers little resistance to the passage of air   When the water manometer is used in measuring the dynamic

intrapleural pressure, a considerable lag occurs as a result of the inertia of the column of water. The lag may be so great as to make it impossible to follow the pressure changes when the respirations are rapid and the oscillations great. Pressure determinations by the water manometer method may be fairly accurate if respirations are slow. Two methods have supplanted the water manometer in our laboratory. One consists in recording pressure changes on a moving photographic film by means of a beam of light reflected from a mirror attached to a rubber diaphragm, while the other utilizes the Singer-Phillips pneumothorax machine (111). This instrument has a sensitive manometer mounted on fine jeweled bearings and gives accurate determinations without any appreciable lag even when the respirations are rapid. It has, however, a definitely limited range of activity, and although it serves well for ordinary intrapleural pressure determinations, cannot record maximum pressures.

The place where the needle is inserted and the position of the patient are important factors to be considered. We measure the intrapleural pressure through the fifth intercostal space in the midaxillary line with the patient in the prone position. Christie (32) recommends the second and third interspace in the midclavicular line, pointing out that in this location the excursions of the visceral pleura over the parietal are small and the danger of rupturing the lung is lessened. We believe, however, that the insertion of the needle into this location has a bad psychic effect upon the patient in that he observes the procedure, and is also undesirable because of the proximity of the needle to the apex of the lung. As will be noted later, the position of the body has a profound influence on the intrapleural pressure.

The apparatus should always be adjusted so that there is a free communication with the pleural cavity. This is indicated by the fact that the intrapleural pressure oscillations correspond to the respiratory movements both in amplitude and in type of curve. Christie (32) recommends the simultaneous registration of the tidal air and the intrapleural pressure as a means of controlling the accuracy of the pressure determinations. This is desirable although not essential. We have found that direct readings made from a Singer-Phillips pneumothorax machine and a Siebe-Gorman spirometer are accurate and are read with sufficient ease to detect any lack of correspondence

Even with the best technique, measurements of intrapleural pressure are accompanied by some danger Although they may be of considerable clinical importance, their detailed study in man should be done only by those experienced in the dynamics of the chest

III Influence of age

At birth the lungs completely fill the thoracic cavity and do not collapse even when the chest is opened. Under such circumstances there can be no elastic recoil and no negative intrapleural pressure (87) Breathing is accomplished solely by the cohesive force of the moistened pleural surfaces During development the thorax enlarges more rapidly than the lungs and the elastic tissue of the lung increases so that a negative tension is developed Growth of the chest and increase in elastic tissue continues until about the twentieth year when the maximum vital capacity and maximum negative intrapleural pressure are probably attained During the fourth decade there is a gradual reduction both in vital capacity and in the ability of the individual to lower his intrapleural pressure Analysis of results obtained by us from normal individuals of varying ages reveals that the changes may be due to two factors, namely, a decrease in the power of the respiratory muscles, and a loss of elasticity of the lungs The latter factor leads to an increase in size of the lungs

IV Effect of position

Aron (4) in 1891 demonstrated that changes in the position of the chest may cause variations in the intrapleural pressure He measured the pressure in one individual and demonstrated that it was more negative in the upright than in the recumbent position This observation has been confirmed by Prinzmetal and Kountz (104) and by Christie (32) The average increase in intrapleural pressure in seven patients with therapeutic pneumothorax was an increase of 2 7 cm. of water when changing from the upright to the recumbent position In six patients with orthopnea the change was even greater, being 4 5 cm. of water more positive in the recumbent position Postural variation is due to a higher position of the diaphragm and a relative mechanical disadvantage in recumbency Limitation of the activity of the muscles of respiration produces less stretch on the elastic lung tissue,

and a less negative intrapleural pressure is developed   The signifi-
cance of this change in relation to the pathogenesis of orthopnea will
be discussed later

We have recently found differences in the two intrapleural pressures
in the lateral recumbent position, the pressure in the uppermost pleural
cavity being much more negative than that in the lower side   This
difference is usually about 3 to 5 cm of water, due to the shift of the

TABLE 1

SEX	AGE	DIAGNOSIS	ORTHOPNEA	INTRAPLEURAL PRESSURE IN CENTI METERS OF H₂O				AVERAGE CHANGE IN CENTI METERS H₂O
				Upright		Recumbent		
				Insp	Exp	Insp	Exp	
Г	49	Emphysema	Moderate	−8	0	−10	+6	+4
M	26	Asthma	Marked	−16	−12	−8	−4	+10
					One minute later	−6	−2	
M	43	Emphysema	Marked	−4	−1	−2	+1	+2
M	65	Cardiac	Moderate	−8	−6	−3	−2	+4 5
M	60	Cardiac	Marked	−7	−4	−2	0	+4 5
M	50	Cardiac marked ascites	Moderate	−6	+4	−4	+6	+2

Average for group 4 5 cm H O more positive in recumbent position

M	26	Case 2 (without asthma)	No	−5	−2	−3	−2	+1
M	33	Tb with pneumothorax	No	−8	−2 5	−3 5	−1 5	+2 75
M	25	Tb with pneumothorax	No	−5	−1	−3 5	+1	+1 75
M	27	Tb with pneumothorax	No	−14	−4	−8	−1	+4 5
M	30	Tb with pneumothorax	No	−7	−2	−6	0	+1 5
M	35	Tb with pneumothorax	No	−14	−4	−8	0	+5
M	30	Tb with pneumothorax	No	−4	0	−2	+3	+2 5

Average for group 2 7 cm H₂O more positive in recumbent position

mediastinum with resulting enlargement of the upper side and en-
croachment on the dependent side   There is thus a greater stretch on
the upper lung and a more negative intrapleural pressure

This observation, which appears not to have been made previously,
is of clinical importance in pneumothorax resulting from accidental or
spontaneous rupture of the lung   In the rare accident in which the
lung was punctured by a trocar we were able to arrest completely the
formation of a pneumothorax by having the patient lie on the injured

side   Such results might also indicate that patients with tuberculosis should be trained to sleep and rest on the involved side in order to reduce the activity of the lung

V Intrapleural pressure in different parts of the chest

There has been some difference of opinion regarding variations in intrapleural pressure in different parts of the pleural cavity   Certainly with a large pneumothorax the pressure is the same in all parts of the cavity   If the contention of Wirz (126) and Christie (32) that the lung elasticity is perfect be true, one would expect the pressure under normal circumstances to be the same throughout   Meltzer (91), however, has found that pressure in the posterior mediastinum varies considerably in different areas, being most negative at the base and becoming less negative as the apex is approached   We have obtained similar results, especially in diaphragmatic breathers   These differences in the intrapleural pressure over various areas of the lung in the normal chest are so small as to be of no practical significance   The presence of adhesions in the pleural cavities may modify pressure relations

D RELATIONSHIP OF INTRAPLEURAL PRESSURE TO PHYSIOLOGICAL PROCESSES AND TO SURROUNDING STRUCTURES

I Circulation of blood

Apart from the importance of the intrapleural pressure in respiration little attention has been directed to the other functions   Carson (27) was the first to consider that it might play an important rôle in circulation   Its influence may be considered under four headings   the effect on the venous pressure and the venous return to the chest, the effect on the heart, the effect on the pulmonary circulation, and the effect on the arterial blood pressure   Although these will be treated separately, they are closely interrelated

(a) *Effect on the venous circulation*   Experiments indicate that the negative intrapleural pressure plays an important part in the return of blood to the chest by producing suction on the great veins entering the thorax   This is especially true during inspiration when the pressure is most negative   The return flow of blood from the abdomen into the

thorax is further aided by elevation of the intra-abdominal pressure on descent of the diaphragm

Wenkebach (122) states that the type of respiration has some influence on venous return   With pure abdominal breathing the rise in intra-abdominal pressure, due to descent of the diaphragm, is an important aid to the return of blood through the inferior vena cava With pure costal breathing this factor is not operative

As pointed out by Kountz, Alexander and Dowell (80), and others (92), in both the experimental animal and man, a less negative intrapleural pressure causes an elevation of the venous pressure by impeding the return of blood to the chest   This fact has been confirmed by the recent experiments of Coonse and Aufrank (40)

In normal individuals respiratory variations in venous pressure are ordinarily not transmitted to the arm veins, because of the inertia of the column of blood between the central and the peripheral veins (120)   Excessive respiratory effort, however, may lower the peripheral venous pressure from 1 to 3 cc of water or even more (11) Respiratory oscillations may occur in the peripheral veins if the venous pressure is considerably raised   In the Valsalva experiment the venous pressure may rise to 42 cm of water (92)   This results from the rise in intrapleural pressure which prevents blood from entering the thorax   The venous pressure continues to rise so long as the experiment is continued   Since the venous return is greatly reduced, the arterial blood pressure falls markedly until it may become imperceptible   When the glottis is opened and the intrapleural pressure returns to its normal level, a greatly increased amount of blood is returned to the heart from the engorged veins, and there is a rise in the systemic arterial pressure (44)

Straining on defecation, heaving, lifting, and other similar acts are modified forms of the Valsalva experiment   Sudden deaths following exertion in patients with limited cardiac reserve may in part be due to the inability of the heart to withstand the greatly increased venous return after relaxation of the expiratory muscles (55)

In the Mueller experiment the peripheral venous pressure first falls as a result of the extremely negative intrapleural pressure which sucks the blood into the great veins of the thorax (55)   A decrease in intrapleural and venous pressures may occur at the onset of bronchial

obstruction, such as occurs in asthma, if emphysema is not an accompanying clinical feature (101)

(b) *Effect on the heart* The negative intrapleural pressure is readily transferred through the pericardium, and the intrapericardial pressure is therefore normally subatmospheric The efficiency of the heart has been found to be greatest at the normal subatmospheric pressure (10) Changes in pressure in either direction, more positive or more negative, have a deleterious effect on the circulation Since the walls of the great veins and auricles are thinner than those of the other vascular channels, changes in external pressure are first reflected on these structures This has been shown by measuring the pressure in the left auricle, which during inspiration is from -2 to -5 mm of water, whereas during expiration it may rise to $+6$ to $+38$ mm of water (123)

With increase in intrapleural pressure the return flow of blood is blocked at its entrance into the chest while with increased intrapericardial pressure the block occurs at the entrance of the great veins into the pericardial cavity and has been designated by Rose "cardiac tamponade" (107) Pressures above atmospheric are not essential to produce cardiac tamponade which may occur when the heart is exposed to atmospheric pressure It is believed that this influence on the hearts of patients with low cardiac reserve may lead to an acute cardiac failure when the organ is exposed to atmospheric pressure during some forms of thoracic surgery (10)

The recent work of Coonse and Aufrank (40) shows clearly the effect of changes in the intrapleural pressure on the heart in the dog. With a less negative pressure they have demonstrated a diminution in the size of the heart and an increase of the heart rate while with more negative intrapleural pressure an increase in cardiac size and a slower heart rate are evident

Changes in intrapericardial pressure may be acute or chronic (9) When an increase in tension occurs suddenly the circulation is immediately slowed and the peripheral veins are congested In a short time the venous pressure may rise above the intrapericardial pressure and the circulation is again restored None of the peripheral signs such as ascites, enlargement of the liver or edema are seen because continuance of increased pressure causes death

If the rise of the intrapericardial pressure takes place slowly, the better known syndrome of "chronic increased intrapericardial pressure" occurs (9) The venous pressure becomes very high, approaching that of right ventricular failure Signs associated with congestive failure such as palpable liver, edema, and dyspnea on exertion are usual Kountz, Alexander and Dowell (80) have found identical symptoms and signs in emphysematous patients with chronically increased intrapleural pressure although in these cases dyspnea is usually more severe

Changes in the electrocardiogram due to the tamponade effect have never been considered to be characteristic Katz (77) and his associates have described changes in the ST interval similar to the changes described by Kountz (82) in anoxemia of the heart Such changes have also been found after rupture of the auricles (36) and have been experimentally produced by injection of fluid into the pericardium (106)

The effect of increased negative intrapleural pressure on the heart has not been so thoroughly studied Chillingsworth and Hopkins (30), who placed dogs in a negative pressure chamber, found that when the negative pressure was greatly increased the arterial blood pressure fell to zero This was attributed to an interference with the pulmonary circulation and to a diminution in the flow of blood to the left heart Other factors entering into such an experiment have made it difficult to evaluate the results In experimentally produced bronchial obstruction with its consequent increase in negative pressure, dilatation of the right heart has been noted (84) When obstruction has been continued over long periods, hypertrophy of both the left and the right heart occurs, due, in part, it is believed, to associated anoxemia (84)

Abnormal variations in intrapleural pressure may cause fluctuations in cardiac size A decrease in the size of the heart during acute elevations of the intrapleural pressure has been noted by fluoroscopic examination This is due to a diminution in the amount of blood flowing into the heart and also to an increase in pressure on the auricles

The inspiratory phase of breathing during an asthmatic attack is accompanied by a greatly increased negative pressure (101) When this occurs we have observed under the fluoroscope an increase in

cardiac size during inspiration and a return to normal during expiration   Coonse and Aufrank (40) have found the same changes in cardiac size in dogs during acute experiments.

(c) *Effect on pulmonary circulation*   Since the small capillaries of the alveoli are relatively thin walled, changes in the intrapleural pressure affect the capillary bed   During inspiration as the pressure becomes more negative, distention of the pulmonary vessels takes place. During expiration the pulmonary capillaries become smaller   Because of the change in caliber of the vessels it has been estimated that at the height of inspiration the lungs may contain one-twelfth of the total volume of blood, an amount which is diminished during expiration to one-fifteenth or one-eighteenth of the total (114)

Definite changes in the pulmonary arterial pressure occur with respiration, both systolic and diastolic pressures falling during inspiration and rising during expiration   Wiggers (123) found changes of about 12 mm of mercury in the systolic pressure and of 8 mm in the diastolic   During apnea the systolic pressure is reduced and the diastolic pressure is elevated   In addition to the changes in blood pressure, Wiggers (123) has shown variations in the contour of the pulse

The fall in pulmonary arterial pressure during inspiration has been attributed by Cloetta (35) to the radial traction of the alveoli which increases the lumen of the pulmonary capillaries during ordinary inspiration   With great distention of the alveoli, however, a linear extension and subsequent narrowing of the pulmonary capillaries occurs, which results in increased resistance to the blood flow

Little is known about the effect of abnormal changes in intrapleural pressure on the pulmonary circulation in the intact chest   With decreased negative pressure, however, it may be said that the blood flow to the lung is diminished   This may be demonstrated in the living man by insertion of a catheter through the cephalic vein into the right auricle   By injection of a concentrated solution of sodium iodide or thorotrast the main pulmonary vessels are visualized by x-ray (28)   If such an injection is made during inspiration when the intrapleural pressure is high, the vessels will be smaller and longer than if it is made during expiration when the intrapleural pressure is more negative

In the presence of a pneumothorax, a procedure which decreases the negative pressure, a great diminution of the blood flow of the collapsed lung has been demonstrated by Chillingsworth and Hopkins (30), and has been confirmed by Corper, Simon and Rensch (42), and others Dock and Harrison (45) found that the reduction in the blood flow
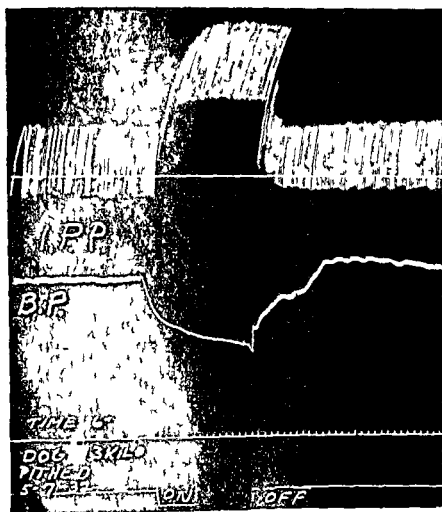

FIG 1 KYMOGRAPHIC TRACING OF A PITHED DOG UNDER ARTIFICIAL RESPIRATION SHOWING THE EFFECT IN INCREASED INTRAPLEURAL PRESSURE ON BLOOD PRESSURE

Intraplentral pressure was increased by an adjustment of the artificial respiration

through the collapsed lung was gradual and that about three days elapsed before the maximum effect was obtained

(d) *Effect on arterial blood pressure* That respiration causes variation in blood pressure in man has been appreciated for over two hundred years There is some confusion in the literature concerning the subject because of the multiplicity of factors and because of conflicting evidence Frederick (125) was the first to point out that at least two distinct and opposing factors are present during respiration

In man during the early part of the inspiratory phase there is an increase both in the cardiac output and heart rate with an increase in blood pressure   Towards the end of inspiration there is a lowering of the blood pressure associated with a decrease in the cardiac output and heart rate   During the latter phase the intrapleural pressure reaches its maximum negativity   The capillaries of the lungs during the period of maximum distention are thus capable of retaining more blood, with the result that there is a decrease in the return of blood to the left heart and a fall in peripheral blood pressure (123)

Lewis (85) has shown that in man the respiratory waves of the blood pressure are dependent mainly on the type of respiration   During costal respiration a fall of blood pressure takes place during inspiration, while in the diaphragmatic or abdominal breathing a rise occurs presumably as a result of the increased venous return through the inferior vena cava during diaphragmatic descent   These observations have not been confirmed by Erlanger (52), who found a fall in blood pressure in both types of inspiration

The phenomenon of pulsus paradoxus has been attributed by Katz and Gauchat (77) to an increase in the intrapericardial pressure which holds the blood in the peripheral veins   Theoretically at least, such a phenomenon could also come about by an elevation of the intrapleural pressure *   These authors have reproduced the condition experimentally by injections of increasing amounts of fluid into the pericardial cavity of animals breathing naturally with the thorax closed They found that the slight decrease in blood pressure which occurs normally during inspiration becomes more and more pronounced until finally the pulse disappears   The explanation has been offered that the disappearance is due to obstruction of the return flow of blood to the heart by fluid in the pericardium   Normally the intra-auricular pressure is subatmospheric during inspiration (123) because of the increased negative pressure in the thoracic cavity   In the presence of increased intrapericardial pressure the intraauricular pressure is above atmospheric at all stages of respiration   During expiration the pres-

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* Head has recently observed marked respiratory variations in blood pressure in patients with greatly increased intrapleural pressure

(Head, J R   Effect of High Intrapleural Pressure on Blood Pressure, Arch Int Med *56*, 904, 1935)

sure in the pulmonary veins is great enough to overcome the auricular pressure and the blood enters the cavities of the heart, but during inspiration the pressure in the intrathoracic veins is further reduced so that little or no blood enters the heart and the arterial blood pressure falls

II Circulation of lymph

It was first suggested by Emerson (50) and later demonstrated by Dolly and Weiss (46) that the negative intrapleural pressure is of great importance in the return of lymph from the abdominal cavity into the thoracic portion of the duct   During inspiration the more negative tension favors the entry of lymph into the thorax   Since the valves of the thoracic duct prevent its backward flow it is forced into the subclavian vein during expiration   Anything which interferes with the respiratory movements will hinder the flow of lymph   Thus by the experimental production of a large pneumothorax, a marked reduction in the lymph flow can be demonstrated in experimental animals (46)   The benefit resulting from pneumothorax in the treatment of lobar pneumonia may perhaps be attributed to a reduction of lymph flow from the lung with a resulting decrease in absorption of toxic products

III Formation of pleural exudates and transudates

Graham (64) observed the remarkable rapidity with which pleural exudates and transudates were formed when the pleural was infected with hemolytic streptococci in pneumonia associated with influenza He pointed out that in this type of pneumonia the dyspnea is extreme and that the maximum respiratory efforts are necessary to maintain an adequate respiratory exchange   He believed that under such conditions the fluid might be sucked out of the lung by the negative intrapleural pressure   By means of an artificial thorax constructed of a bell jar and a pair of lungs he found the assumption to be true   It was observed that the fluid poured out more rapidly during expiration He therefore suggested that during inspiration the subpleural lymphatics became filled by the negative intrapleural pressure and during expiration the fluid was actually squeezed out of them   Brock and Blair (22) have confirmed Graham's observations in living lungs, using

the heart-lung preparation They showed further that when the respiratory rate was increased there was a more rapid accumulation of fluid This was suggested by Graham from clinical observation Brock and Blair also showed that not only the rate of formation but also the rate of absorption of pleural exudate depended upon the force of the respiratory movements With labored respiration the removal of fluid took place rapidly but with quiet breathing absorption was slow

IV. Influence upon the mediastinum

Since the mediastinum is separated from the pleural cavity only by a thin layer of pleura, the negative intrapleural pressure is readily transmitted to it Assman (5) has stated that the pressure within the mediastinum is atmospheric pressure minus that due to retraction of the lung By direct measurement in the posterior mediastinum of rabbits, Meltzer (91) found the pressure to be negative Rosenthal and Leube (108) found the esophageal pressure likewise to be sub-atmospheric The negative pressure in the mediastinum is of considerable clinical importance It is responsible for mediastinal emphysema which follows operations on the thyroid gland or other surgical procedures at the base of the neck (24). Likewise accidents in which iodized oil is accidentally injected about the trachea instead of into it are made more serious by the fact that the lowered mediastinal pressure causes a descent of the oil into the mediastinum

Increase in the mediastinal pressure results in changes which are similar to those following cardiac tamponade Ballon and Francis (8) have pointed out that the most common cause of such a condition is mediastinal emphysema, although tumors and inflammatory processes may produce a similar picture Since the great vessels and trachea come directly through the mediastinum, changes in the mediastinal pressure have an even more direct effect on these structures than changes in intrapleural pressure Ballon and Francis (8) have studied this by inserting a rubber balloon into the mediastinum of rabbits Upon inflation of the balloon they found a fall in arterial blood pressure, a rise in venous pressure and a diminution in respiration

Change in mediastinal pressure most readily affects the thin-walled

vessels   Thus the venae cavae are more readily influenced than the intrathoracic arteries   The relatively rigid trachea and bronchi are not notably compressed

Ballon and Francis (8) have found in experimental animals that increase in mediastinal pressure produced by mediastinal emphysema causes a less negative intrapleural pressure

V Relationship to intra-abdominal pressure

Considerable experimental work has been done on intra-abdominal pressure and its relationship to pressure within the chest   Conflicting results have been recorded   It is believed by some that the intra-abdominal pressure is slightly above that of the atmosphere (50)   Small variations from atmospheric pressure should have little effect on breathing, but it is of great importance for efficient respiration that there should be a marked difference in pressure between the pleural and peritoneal cavities and that the pressure in the pleural cavity should be more negative   Elevation of the diaphragm during expiration depends on this pressure difference without which diaphragmatic movements would be greatly limited

Changes in the normal pressure relationships may occur in two ways   The intrapleural pressure may become less negative as in emphysema (80) so that it more nearly equals the intra-abdominal pressure, or the intra-abdominal pressure may fall so that it approaches the negativity of the intrapleural pressure   Inability of the individual to maintain a proper relationship between the pressures above and below the diaphragm throughout all periods of the respiratory cycle may occur in visceroptosis, where the pressure in the upper abdomen is more negative than normal (50) and thus the pressures on the two sides of the diaphragm tend to approach each other   By raising the intra-abdominal pressure with an abdominal belt the normal pressure difference is established with a resulting increase in the vital capacity   Likewise in emphysema, as will be pointed out later, the intrapleural pressure approaches atmospheric, and the pressure difference between the two cavities is again reduced   Thus such patients have difficulty with breathing, due in part at least to the limitation of the ascent of the diaphragm   By use of an abdominal belt, the intra-abdominal pressure may be raised above the intrapleural pressure, allowing the

diaphragm to return to a more nearly normal expiratory position. By utilizing this principle, considerable relief may be afforded in some patients with either emphysema or visceroptosis (1, 32)

There is some dispute as to the relationship between changes of intrapleural and intra-abdominal pressure Some have found that the pressures change synchronously, that is, both are more negative during inspiration, others find that during inspiration the abdominal pressure rises Our observations substantiate those of Paul Bert (13), who has adequately explained the reason for the discrepancy obtained by different observers He points out that the change in the abdominal pressure depends upon the type of respiration When the respiration is mainly abdominal or diaphragmatic, the descent of the diaphragm causes an increase in the abdominal pressure during inspiration and a decrease during expiration If the respiration is mainly intercostal or thoracic, the elevation of the costal margins causes distention of the abdominal cavity and a more negative abdominal pressure during inspiration Under such circumstances the abdominal pressure fluctuates in the same direction as the pressure in the thoracic cavity

Lewis (85) has shown in the experimental animal the importance of diaphragmatic activity in maintaining the normal pressure relations of chest and abdomen With normal respiratory activity and descent of the diaphragm he records a rise in the intra-abdominal pressure during inspiration If both phrenic nerves are cut and the diaphragmatic activity is eliminated, there is an immediate change in pressure relationship, and the intra-abdominal pressure now closely follows the intrapleural pressure

Consideration of these observations leads to an explanation of the mechanism of the so-called paradoxical motion of the diaphragm In conditions where the diaphragm has undergone loss of tone as in section of the phrenic nerves and some forms of emphysema, inspiration is thoracic During inspiration both the intrapleural pressure and the intra-abdominal pressure become less, but the decrease in the intrapleural pressure is greater than the change in the intra-abdominal pressure Consequently the diaphragm rises during inspiration and falls during expiration

Changing the intra-abdominal pressure has an immediate effect on

respiration   Prinzmetal, Brill, and Leake (103) have shown in normal animals with normal abdominal tension that raising the intra-abdominal pressure (fig 1) causes a rise in the intrapleural pressure   Hamburger, Heinricius and Coombs (39) have demonstrated that a marked rise in intra-abdominal pressure causes a progressive diminution in respiratory activity until finally the animal dies of respiratory failure The explanation for this result is that the diaphragm rises but does not descend   Increase in abdominal pressure may also limit excursion of the chest wall since elevation of the diaphragm presses the lungs outwards thereby maintaining the chest in the inspiratory position

In late pregnancy a moderate rise of the intrapleural pressure takes place owing to ascent of the diaphragm, and may be one factor which causes respiratory difficulty   Following surgical operations an increase in the intra-abdominal pressure takes place with a less negative intrapleural pressure (103)   This fact may be partly responsible for respiratory difficulty under such circumstances   In marked ascites there is also an increase in the intra-abdominal pressure and a decrease in the negative intrapleural pressure   In a case of cirrhosis of the liver with ascites we found an intrapleural pressure of -4 cm of water during inspiration and a $+6$ cm of water during expiration

E FACTORS PRODUCING ABNORMAL VARIATIONS IN INTRAPLEURAL PRESSURE

I Increased respiratory activity

(a) *Increased carbon dioxide tension*   Increase in carbon dioxide tension, produced experimentally by introducing various concentrations of carbon dioxide through a tracheal cannula, always causes a more negative intrapleural pressure (20)   This is the result of the increase in depth of inspiration following stimulation of the respiratory center   The increase in negative pressure is in direct proportion to the concentration of carbon dioxide inhaled   This change in intrapleural pressure is accompanied by an increased thoracic girth   With high concentrations of CO_2, expiration changes from a passive to an active movement with the result that the intrapleural pressure at the height of expiration may become positive   The increase in pressure at the height of expiration, however, is never so great as the fall during inspiration (20)   The significance of these pressure changes in the

therapeutic utilization of carbon dioxide in pulmonary subventilation will be discussed later

(b) *Anoxemia* Experimental anoxemia produced in dogs by rebreathing through a spirometer with soda lime in the circuit to absorb the carbon dioxide has essentially the same effect upon the intrapleural pressure as increased alveolar carbon dioxide tension (105) There is first an increase in inspiratory muscular effort and a decrease in intrapleural pressure When the anoxemia becomes extreme, active expiratory motion ensues and the pressure becomes positive at the height of expiration The increase in negative pressure is, however, never so great as the decrease

During severe muscular exercise the same sequence of events may be expected An increase in the inspiratory muscular effort will result in an increase in negative pressure When the hyperpnea becomes more extreme, however, active expiration also occurs, and the intrapleural pressure during this phase of respiration will presumably rise above that of the atmosphere

The decreased intrapleural pressure resulting from increased alveolar carbon dioxide, anoxemia, and exercise, is an important factor in aiding increased venous return to the heart The blood flow through the lungs themselves is enhanced by better expansion of the pulmonary capillaries and alveoli

II Effect of bronchodilator drugs

Brill and Leake (19) have shown that bronchodilator drugs, such as epinephrin and atropin cause a less negative intrapleural pressure in dogs The factors probably responsible for this change are dilatation of the bronchi and lowered resistance to the entrance of air into the lung, with resulting increase in distensibility of the lungs Thus the intrapleural pressure at the end of inspiration will be less negative than normal Measurements of the thoracic girth reveal a diminution in size, indicating that the chest is held in a more expiratory position than usual (102)

III Pathological conditions which alter intrapleural pressure

(a) *Incomplete bronchial obstruction* Both experimental bronchial obstruction and clinical attacks of asthma are associated with a de-

crease in the intrapleural pressure   This was first observed in 1908 by
Sir Thomas Lewis (85) during a study of the respiratory waves of the
blood pressure in cats during partial tracheal obstruction   Auer and
Lewis (6) observed the same change in guinea pigs   The observation
was repeated by Smith, Harter and Alexander (113), and by Kountz
(80) and Prinzmetal and others in dogs   Bronchoconstricting drugs,
such as eserine or pilocarpine, have an identical effect (21)   Obstruc-
tion to the trachea of dogs by mechanical devices has been found to
result in a decrease in the intrapleural pressure   The fall is in direct
proportion to the degree of bronchial obstruction (80)

Prinzmetal (101) has shown that during asthmatic attacks in man
the intrapleural pressure is more negative than normal and returns to
the previous level after the attack is over provided severe emphysema
is not present

Example—Intrapleural pressure

	Inspiration	Expiration
During asthmatic attack	−16 cm water	−12 cm water
Following attack	−5 cm water	−2 cm water
Difference	−11 cm water	−10 cm water

One factor which is responsible for the change in the intrapleural
pressure following incomplete bronchial obstruction is the increased
difficulty of air transmission through the bronchi (101)   With
bronchial obstruction and the usual inspiratory effort, less air enters
the lungs and the distensibility is decreased   The lungs, therefore,
do not follow the chest wall as they normally should and a decreased
pressure is created

Another factor is the interference with the respiratory exchange
which may occur during profound bronchial obstruction and which
may produce anoxemia (105) and retention of carbon dioxide (20),
factors in themselves causing a more negative intrapleural pressure
The mechanical factor first mentioned, however, is undoubtedly the
most important since the pressure changes occur before interference
with the respiratory exchange could be expected   The following
diagram will better illustrate the sequence of events following incom-
plete bronchial obstruction

Incomplete bronchial obstruction

Increased resistance
to respiration and
a decreased distensi-
bility of the lung

Accumulation of
carbon dioxide
and anoxemia

Increased inspiratory
muscular effort

Increased negative intra-
pleural pressure
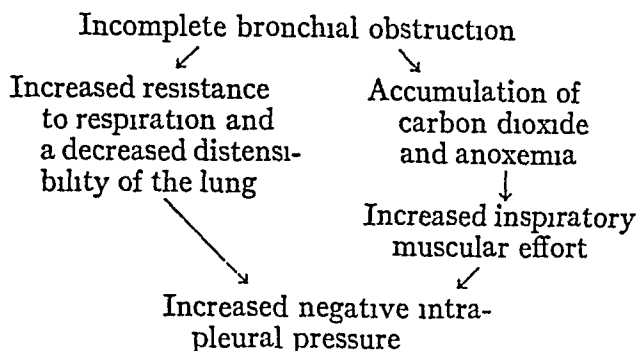
It is commonly stated that the chief effort during the asthmatic attack is expiratory since the intrapleural pressure is more negative especially during inspiration, but it is obvious that the main respiratory effort must be inspiratory (101) Although in the very severe asthmatic attack active expiratory effort occurs, the resulting increase in intrapleural pressure due to active expiratory effort is never so great as the decrease in pressure due to active inspiratory effort During the asthmatic attack expiration is greatly prolonged, but is chiefly passive Asthmatic breathing must not be confused with emphysematous breathing such as occurs in long standing asthma In severe emphysema expiration may no longer be passive but becomes an active muscular effort as is explained later

(b) *Emphysema* The work of Kountz and his associates (80, 83) and of Christie (32) has established that the intrapleural pressure is less negative in patients with emphysema than in normal individuals Christie has pointed out that in the well-advanced disease there is a loss of lung elasticity By simultaneous registration of the intrapleural pressure on the volume of the air inspired by normal individuals, he was able to demonstrate that within physiological limits, the degree of distention of the living lung is proportionate to the change in the intrapleural pressure, and if distention of the lung be maintained, the intrapleural pressure remains at a constant level These observations lead to the conclusions that the elasticity of the lung was perfect Since such is the case, when the lung volume is plotted against the intrapleural pressure, the points fall along a horizontal line, similar to any elastic body In emphysema, on the other hand, a logarithmic curve is obtained characteristic of a non-elastic body in which the same force can produce different degrees of distention, the deviation of the

application of the force being the variant   This work demonstrates conclusively the loss of elasticity in the emphysematous lung

In bronchial obstruction the initial process of lung expansion is associated with an increase in negative intrapleural pressure due to the respiratory effort of drawing air past the obstruction   In expiration, if the force exerted is not sufficient to push the air past the obstruction, air accumulates in the alveoli and the lungs distend   So long as the diaphragm and the chest can expand, they absorb the pressure exerted by the enlarging lungs and the intrapleural pressure remains negative   As the distention progresses however and the size of the lungs becomes equal to or exceeds that of the thoracic cavity, there is a definite rise in the intrapleural pressure, not only during expiration but also during the entire respiratory cycle

The early stage of emphysematous change is shown in the studies of Prinzmetal (101) on animals whose intrapleural pressure was reduced by exposure to an abnormally low atmospheric pressure over long periods   Such animals developed typical emphysema

The same mechanism may also be demonstrated experimentally by inducing anaphylactic shock in guinea pigs and thus creating an intense emphysema from bronchospasm (113)   As the shock begins, there is an increased inspiratory effort with a marked fall in intrapleural pressure   This represents the phase of pulmonary distention as the animal forcibly pulls air through the constricted bronchi   The forces of expiration are insufficient to expel the air, and some of it becomes trapped in the lung with each breath   The lungs enlarge more and more and the diaphragm descends until it can no longer function   Finally an abrupt elevation of the intrapleural pressure occurs, due to the muscular effort to expel air and also to a loss of distensibility of the lung as it increases in size

Christie (32) has shown that one notable feature of the pressure in emphysematous individuals is that it cannot be maintained but reapproaches the atmospheric level when an individual holds his breath after a full inspiration or expiration

(c) *Pneumothorax*   The importance of the intrapleural pressure in pneumothorax is better known and appreciated than in any other condition   This is due not only to its importance in thoracic disease but also to the use of artificial pneumothorax in the treatment of

disease of the chest   This subject has been admirably discussed by Graham in his monograph published in 1924 (63)   Since the principles advocated at that time have now met with universal approval, it will be necessary to consider in this paper only the major points

Two varieties of pneumothorax may be considered the open and the closed form   In the open form there is free communication between the pleural cavity and the outside air through an opening in the chest wall   In closed pneumothorax there is no opening in the chest wall   Closed pneumothorax may be either spontaneous, due to rupture of the visceral pleura, or artificial, which is produced for therapeutic purposes   In both the open and closed forms the intrapleural pressure is usually less negative, owing to the presence of air in the pleural cavity which collapses the lung and reduces the elastic stretch essential for the maintenance of the negative tension   In closed pneumothorax the reduction in negative tension is proportionate to the amount of air in the pleural cavity   In open pneumothorax it is proportional to the size of the opening in the chest wall

In a normal individual the change in the intrapleural pressure resulting from unilateral pneumothorax is reflected upon the contralateral side owing to the shift of the mediastinum   When the mediastinum is fixed by adhesions there is less shift and little change in the pressure in the opposite pleural cavity   Thus patients who have had previous pulmonary disease are better able to tolerate a large pneumothorax than those with a normal mediastinum

Under certain circumstances, notably those associated with rupture of the pleura, a valvular spontaneous pneumothorax sometimes designated as tension pneumothorax may occur   In this condition air is sucked into the pleural cavity during inspiration and cannot escape during expiration, causing pressure to rise considerably above that of the atmosphere   A tension pneumothorax can only occur in a closed chest cavity

Certain physiological differences distinguish an open and closed pneumothorax   In the open form air is sucked through the opening in the chest wall during inspiration due to the decreasing intrapleural pressure   The pneumothorax becomes larger during inspiration and less air passes through the trachea into the lung   This does not occur with closed pneumothorax   Also in the open form, due to the increase

in the amount of air in the pleural cavity during inspiration, there is a shift in the mediastinum during each respiratory cycle which is called "Pendelluft" This shift of the mediastinum is believed to have a deleterious effect upon the heart because of the twisting of the great vessels A slight degree of mediastinal shift usually occurs in closed pneumothorax especially if it has been present for some time This is due to the fact that a greater amount of air enters the normal lung, because the compressed lung becomes progressively less distensible as it remains partially or completely collapsed Thus during inspiration, the mediastinum shifts to the pneumothorax side In open pneumothorax, on the other hand, if during inspiration more air enters through the opening in the chest wall than passes through the trachea into the opposite lung, the mediastinum will shift to the side opposite the pneumothorax This shift of the mediastinum is due to the development of a more negative pressure on the opposite side of the thorax Another factor which makes an open pneumothorax more dangerous than a closed one is loss of body heat through the pneumothorax opening (63)

In open pneumothorax treatment closure of the opening should be made at the end of expiration or better still at the end of a forced expiration in order to expel the air from the pneumothorax cavity and reestablish the negativity of the intrapleural pressure If the opening is closed at the height of inspiration, air will be retained in the pleural cavity, and a closed pneumothorax with an intrapleural pressure less negative than normal will result (20) (fig 3)

The ability of the individual to tolerate an open pneumothorax depends on his vital capacity Graham (65) has shown that when the vital capacity is greatly reduced, a very small opening in the chest may be sufficient to cause death, if the vital capacity is normal, a relatively large pneumothorax may be compatible with life This is especially true if the mediastinum is fixed By permitting patients with empyema following pneumonia to regain normal vital capacity before drainage of the chest cavity, the death rate may be greatly reduced (65)

Graham (63) and Prinzmetal (20) have demonstrated that during pneumothorax there is a mean increase in thoracic girth It has been suggested that this may be a compensatory effort to recreate the normal negative tension (fig 2)
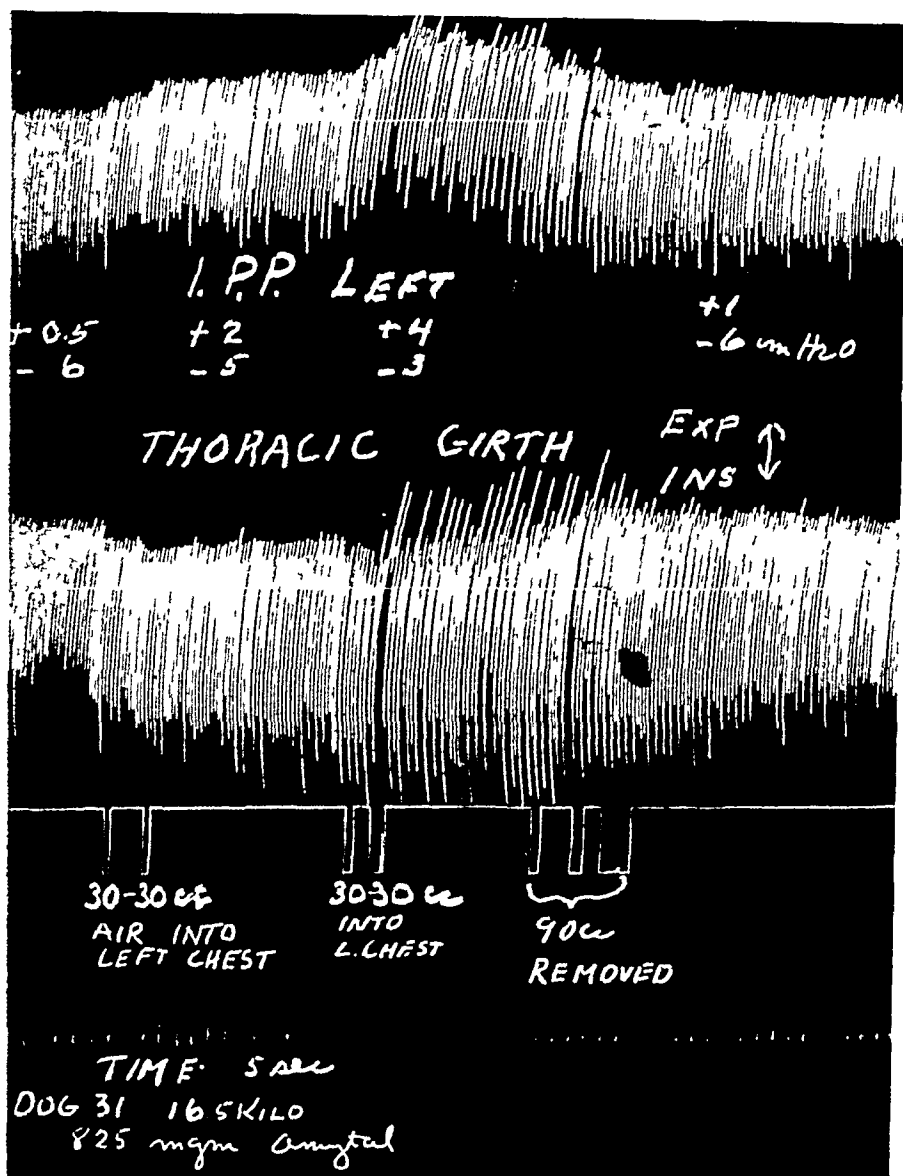
FIG 2 KYMOGRAPHIC RECORD OF INTRAPLEURAL PRESSURE AND THORACIC GIRTH IN A DOG UNDER SODIUM AMYTAL ANESTHESIA SHOWING THE EFFECTS OF THE INJECTION AND WITHDRAWAL OF AIR IN THE PLEURAL CAVITY

In this instance the intrapleural pressure tracing is of the same side of the chest into which the air was injected   Figures indicate intrapleural pressure in centimeters of water
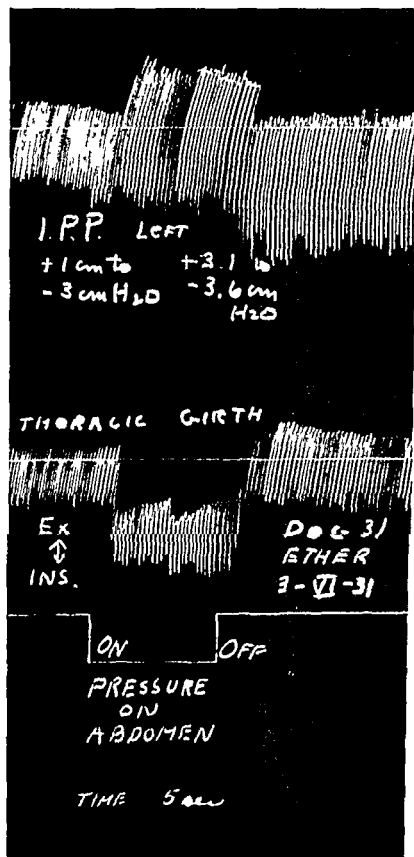
FIG 3 KYMOGRAPHIC RECORD OF INTRAPLEURAL PRESSURE AND THORACIC GIRTH OF A DOG UNDER ETHER ANESTHESIA SHOWING EFFECTS OF PRESSURE ON THE ABDOMEN

The figures indicate intrapleural pressure in centimeters of water

If the lung has been collapsed for long periods of time, as in prolonged therapeutic pneumothorax, it may become fibrotic, have increased elasticity, and lowered distensibility In such cases the intrapleural pressure may be perfectly normal The absorption of some of the air or its artificial removal may produce a great reduction in pressure in spite of the pneumothorax, because the collapsed lung cannot expand and take up the space previously occupied by the air

(d) *Intrathoracic tumor masses and fluid* Graham has shown that not only gas but also hydrothorax and tumor masses in the chest disturb the intrapleural pressures (63) Each operates in a different manner In the absence of adhesions gas produces an equal pressure throughout The pressure effect of fluid is similar to that of fluid under any other circumstances and acts in accordance with the laws of hydrostatic pressure Thus pressure is greatest at the most dependent point and becomes less as the upper border is approached Tumors exert their pressure effects directly wherever they may be located If they cause complete obstruction of a bronchus, atelectasis of the lung occurs and a much more negative intrapleural pressure may result If the obstruction is incomplete, emphysema is usually produced, and the intrapleural pressure may eventually become less negative If they press merely on the lung tissue nothing significant will happen unless the tumor is large and causes considerable pulmonary compression in which case the pressure will become less negative

(e) *Pulmonary subventilation* Pulmonary subventilation results from an elevation of the diaphragm and a limitation of its motion, with subsequent rise in the intrapleural pressure and a decrease in respiratory function It occurs most frequently postoperatively but may also occur in any condition with abnormally elevated intra-abdominal pressure, especially in debilitated individuals

The physical findings of pulmonary subventilation are those resulting from elevation of the diaphragm and associated pulmonary compression The chest is in an inspiratory position, and there is a marked reduction of vital capacity Most frequently breath and voice sounds are diminished, while râles and bronchial breathing may occasionally be found Dyspnea may be present and is attributable to the pressure changes in the chest (23)

It is generally recognized that upper abdominal operations involve procedures which lead to abnormal pressure changes in the chest Recently the factors have been analyzed by Prinzmetal Brill, and Leake (103)   The first is anesthesia, which may cause a decrease in the negative intrapleural pressure even exceeding that of the atmosphere and due in part to paralysis of the intercostal muscles   Another factor is the abdominal incision which further decreases the negative pressure   This has been explained by Overholt on the basis of a pneumoperitoneum (96) (fig 3)   He believes that the intra abdominal pressure is normally subatmospheric and that when the abdomen is opened, air is sucked into the peritoneal cavity just as air is sucked into the pleural space (97)   Finally, traction on an abdominal viscus such as the stomach causes a further decrease in negative tension (fig 4) These changes in intrapleural pressure do not disappear when the operation is completed and the abdomen is closed

Pulmonary subventilation also occurs in other conditions   It may develop in elderly patients who have been bedridden for some time by conditions such as fractures (103)   It also occurs in tympanites, which raises intra-abdominal pressure and elevates the diaphragm Pulmonary subventilation is also present in ascites (104)

Carbon dioxide has been found to be of aid both in the prevention and in the treatment of postoperative pulmonary complications (112)   As has been pointed out above, carbon dioxide causes a more negative intrapleural pressure by increasing the depth of respiration (20)   This tends to lower the intrapleural pressure to its normal level   If atelectasis has already occurred, the increased negative intrapleural pressure induced by carbon dioxide inhalation will help to distend the collapsed lung

(f) *Atelectasis*   In obstructive atelectasis the intrapleural pressure is more negative than in any other pathological condition and in many instances may be as low as minus 40 cm of water (68)   The work of Coryllos and Birnbaum and others (43) has definitely proved that atelectasis results from bronchial obstruction   The mechanism of production of this greatly reduced pressure is as follows   because of obstruction of the bronchus, air is trapped in the lung or in a lobe of the lung   The blood supply to the portion of the lung remains patent for a time at least, and the air is therefore absorbed, leaving the lobe
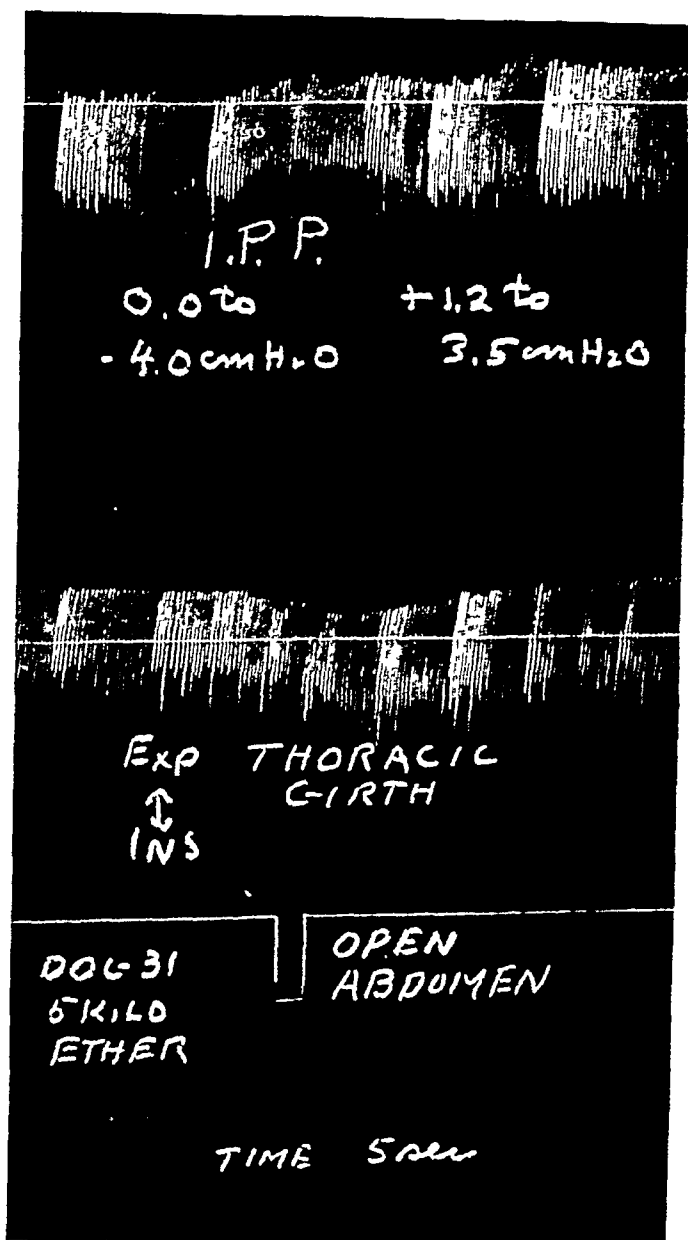
FIG 4 KYMOGRAPHIC RECORD OF INTRAPLEURAL PRESSURE AND THORACIC GIRTH OF A
DOG UNDER ETHER ANESTHESIA SHOWING EFFECTS OF OPENING THE
ABDOMEN

solid (43) Since the atelectatic lobe takes up much less space than a normal lobe, there is greater expansion and stretch in the remaining functional lung tissue and the intrapleural pressure is consequently reduced

Van Allen (116) has shown that in order to produce atelectasis in the normal lung, obstruction to a major bronchus must be present, since there is a collateral circulation between the lobules of the lung He has pointed out that if a smaller bronchus is occluded in a normal lung, the collateral circulation will prevent the collapse of that portion of the lobe by supplying air through the intra-alveolar routes

Because of the increased negative pressure in atelectasis the mediastinum is displaced to the side of the lesion, there is an elevation of the diaphragm and a retraction of the chest wall with limitation of its motion on the affected side These changes are the opposite of those found in pneumothorax since the change in the intrapleural pressure is in the opposite direction

Some of the symptoms are due to the shift of the mediastinum which results in twisting and torsion of the great vessels Because of this Elliot and Dingley (48) suggested that the production of a pneumothorax on the affected side would be of therapeutic value since it would tend to shift the mediastinum to its normal position It should be pointed out, however, that further reduction in the vital capacity might result from the pneumothorax, and the patient's condition might not be greatly benefited

Although in man little is known about the pressure in the pleural cavity opposite the atelectatic lung, it has been shown that in the experimental animal it is reduced All evidence indicates that the pressure changes in man are similar It would be expected, however, that in an individual whose mediastinum is fixed little or no change in the opposite pleural cavity would take place

Atelectasis is one of the conditions in which determination of an increased negative intrapleural pressure may be of diagnostic importance, as is shown by the following case

An eleven year old boy entered the St Louis Children's Hospital complaining of dyspnea, cough and orthopnea He believed that the symptoms resulted from a blow on the chest received a few weeks previous to admis-

sion   Examination revealed the classical signs of hydrothorax on the right side and complete unilateral opacity was found in the x-ray   A needle was inserted into the chest and bloody fluid was removed   Intrapleural determinations revealed a pressure of −20 cm of water   This immediately suggested the presence of atelectasis since there was no other reason for the patient to have such a reduced pressure, especially with a hydrothorax   Since atelectasis is due to bronchial obstruction, it was suggested that a neoplasm obstructed a bronchus on the right side   At autopsy a lymphosarcoma was found in the right main bronchus with atelectasis of the entire right lung

TABLE 2

	ATELECTASIS	PNEUMOTHORAX	PULMONARY SUBVENTILATION
Intrapleural pressure	Reduced	Increased	Increased
Distribution of lesion	Unilateral	Unilateral	Bilateral
Position of the mediastinum	Shifted to the side of the lesion	Shifted to the opposite side	In midline
Position of the diaphragm	Elevated on the side of the lesion	Depressed on the side of the lesion	Elevated on both sides
Thoracic cage	Depressed on the side of the lesion with narrowing of the intercostal spaces	Elevated on the side of the lesion with widening of the intercostal space	Elevated on both sides with a wide subcostal angle

Because of the rather fine distinction between atelectasis, pulmonary subventilation, and pneumothorax, table 2 may be used to demonstrate the different dynamic characteristics of the three conditions

(g) *Pneumonia*   There has been increasing interest in the intrapleural pressure in pneumonia because of the contention of Coryllos and Birnbaum (43) that pneumonia is the result of bronchial obstruction and that the primary lesion is atelectasis   The recent use of artificial pneumothorax in the treatment of pneumonia has offered an opportunity to check this theory (12, 16)   If atelectasis is the essential initial lesion in pneumonia, the intrapleural pressure should be reduced just as it is in ordinary atelectasis   It seems important that

the determinations be made as early as possible in the course of the disease   In a recent case of lobar pneumonia, the intrapleural pressure at the end of the first twenty-four hours of the patient's illness was —6 to —4 cm of water   Blake (16) has recently found in 16 cases of pneumonia that the average intrapleural pressure was —10 cm of water during inspiration and —6 cm of water during expiration   Coghlan (37) found a decreased pressure in some of his cases   We feel that the results obtained by these observers and ourselves are evidence against Coryllos' theory   That some reduction of the intrapleural pressure should occur in lobar pneumonia is inevitable because of the anoxemia which is present during the early stages of the disease and because the exudate in the bronchi will increase the resistance to air entering the lung   Certainly in our experience and in that of other observers the great reduction of the intrapleural pressure that accompanies atelectasis was not found   In pneumonia these observations raise a question as to the validity of the atelectasis theory of pneumonia

(*h*) *Cardiac decompensation*   Christie and Meakins (34) have recently made simultaneous tracings of the intrapleural pressure and of the tidal air in several cases of congestive heart failure   In all such cases they found that the intrapleural pressure is increased and frequently rises above atmospheric pressure at the end of expiration   In two patients with uncomplicated cardiac decompensation we found the intrapleural pressure to be —8 to —6 cm of water and —7 to —4 cm of water in a sitting position   In the recumbent position, however, the pressures rose to —3 to —2 cm of water and —2 to 0 cm of water   Christie and Meakins (34) have further found that the tidal air was considerably reduced with the normal intrapleural pressure fluctuations   Thus, the distensibility of the lung in cardiac decompensation is considerably reduced   They also believe that there is some impairment in pulmonary elasticity in congestive failure   The decrease in the negative intrapleural pressure can be expected to raise the peripheral venous pressure and cause further venous stagnation

(*i*) *Orthopnea*   The etiology of this common symptom has been the subject of many investigations   In view of the variety of clinical conditions which are associated with orthopnea, it is probable that no one factor can explain its mechanism in all cases   It is one of the most

striking symptoms of cardiac decompensation, particularly of the type associated with failure of the left ventricle and resulting pulmonary congestion It is also found in a variety of pulmonary conditions Any process which greatly diminishes pulmonary volume is often associated with orthopnea Thus it is commonly present in emphysema, hydrothorax, pneumothorax, and many allied conditions During the asthmatic attack orthopnea is invariably present Such conditions as tumors of the anterior or posterior mediastinum may cause it Any condition which increases the intra-abdominal pressure and causes the diaphragm to encroach upon the pulmonary space is a common cause

It is not the function of this paper to discuss the causes of orthopnea but only to point out the relationship that they bear to the pressure changes in the chest Much support has been given to the idea that pulmonary ventilation is facilitated in the upright position It has been pointed out that the vital capacity is generally higher in the sitting position not only in normal individuals but also in patients with orthopnea due to various causes Peabody (98) has shown that the reduction in vital capacity in patients with cardiac decompensation is often proportional to the degree of myocardial insufficiency It is therefore held that these patients seek the upright position to increase their reduced vital capacity Haldane and his associates point out that in the upright position the lungs expand more evenly and respiration is generally more efficient Bohr (18) found a greater mid-capacity while Hurtado and Fray (76) found an increase in total lung volume and an increase in residual air in the upright position

Aron (4) found in one normal individual that the intrapleural pressure was increased in the recumbent position, an observation confirmed by Prinzmetal and Kountz (104) and by Christie and McIntosh (33) We extended the studies to patients with orthopnea In 6 patients with orthopnea due to various causes the intrapleural pressure was found to be elevated in the recumbent position Of the cases studied, 2 had uncomplicated cardiac decompensation, 1 had cardiac decompensaton with cirrhosis of the liver and marked ascites, 2 had severe emphysema while 1 was in an asthmatic attack at the time the intrapleural pressure was determined In the cases with orthopnea the intrapleural pressure was more positive in the recumbent than in

the upright position, the average change being 4 5 cm of water   In a group of normal patients without orthopnea the pressure was more positive in the recumbent position by 2 7 cm of water   In the group with orthopnea the average intrapleural pressure at the end of expiration was plus 1 5 cm of water   In the upright position, however, the average pressure of these patients was reduced to −3 2 cm of water   A positive intrapleural pressure in these patients, such as occurs in the recumbent position, should impose further difficulty on the cardio-respiratory system   The positive pressure would not only disturb the pulmonary circulation but, as has been pointed out, it would also diminish cardiac function   In the presence of myocardial damage a positive pressure can be expected to have a still more deleterious effect (10)   By assuming the upright position the intrapleural pressure of these patients is reduced and becomes subatmospheric, thus greatly increasing the efficiency of the circulation and respiration

SUMMARY

The mechanism of the development of negative or subatmospheric pressure in the pleural cavities is considered

The intrapleural pressure is normally modified by age as well as by position of the body   In the upright position it is more negative than in the recumbent, while in the lateral recumbent position the pressure in the uppermost chest is more subatmospheric than in the lower side   The importance of the observation in the treatment of certain pulmonary diseases is considered

Intrapleural pressure plays an important rôle in the physiology of the circulation of the blood   We have considered in detail its effect on the systemic venous and arterial pressures, the pulmonary circulation and on cardiac function   The nature of pulsus parodoxicus is shown to be associated with increased pericardial or intrapleural pressure

The negative intrapleural pressure aids the flow of lymph in the thoracic duct and the lymph drainage of the lung itself and is of significance in the formation of pleural exudates and transudates

The relationship of the pressure in the pleural cavity to the pressure in the mediastinum and the pressure in the abdominal cavity is of importance in the normal function of the diaphragm, which is enabled

to rise during expiration when the intrapleural pressure is more negative than the intra-abdominal pressure   If the pressures in the abdominal and pleural cavities tend to become equal as they do in emphysema and in visceroptosis, there is great limitation of diaphragmatic motion By increasing the intra-abdominal pressure by means of an abdominal belt, the normal pressure difference between the two cavities tends to be reestablished and improvement in the motion of the diaphragm and a higher vital capacity results   The mechanism of paradoxical motion of the diaphragm is shown to be due in part to less negative intrapleural pressure

Factors producing abnormal variations in intrapleural pressure are considered   Increased carbon dioxide tension and anoxemia create a more negative tension in the chest due to stimulation of inspiration with a resulting mean increase in size of the thorax   Bronchodilator drugs cause a less negative intrapleural pressure

Intrapleural pressure in pulmonary disease is an important consideration.   Incomplete bronchial obstruction whether produced by bronchoconstricting drugs, or by an asthmatic attack in man causes a more negative intrapleural pressure   The increased negative pressure during the asthmatic attack clearly demonstrates that the dyspnea in asthma is mainly inspiratory and not expiratory as is commonly believed   The factors responsible for the increase in negative pressure during the asthmatic attack are increased resistance to respiration and decreased distensibility of the lung   Accumulation of carbon dioxide and anoxemia may also play a part   All these factors experimentally increase the negative tension

The pathogenesis of emphysema following bronchial obstruction is considered   The complete loss of pulmonary elasticity in emphysema is responsible for the fluctuation of the intrapleural pressure around atmospheric pressure in spite of great respiratory effort

The intrapleural pressure changes in pneumothorax are discussed The mechanism of the respiratory shift of the diaphragm in both the open and closed form of pneumothorax is demonstrated   The pressure changes in pulmonary subventilation, especially the type following abdominal surgery, are demonstrated   Anesthesia, abdominal incision, and traction on an abdominal viscus cause a less negative intrapleural pressure   In atelectasis the negative pressure is more

increased than in any other condition and the measurement of the intrapleural pressure in this condition is of diagnostic significance The atelectasis theory of lobar pneumonia would not appear entirely satisfactory because the great increase in negative pressure found in atelectasis is absent in lobar pneumonia   In cardiac decompensation the intrapleural pressure is less negative than normal

The relationship of pressure changes in the chest in the upright and recumbent positions to the pathogenesis of orthopnea is considered It is suggested that orthopnea is in part at least the result of intrapleural pressure changes

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